



## Clinical trial results:

**A randomised placebo-controlled study of the safety and tolerability of a retinoid-X receptor agonist's ability to promote remyelination in people with relapsing-remitting multiple sclerosis already on interferon-beta therapy: a phase 2a trial**

### Summary

EudraCT number	2014-003145-99
Trial protocol	GB
Global end of trial date	17 May 2019

### Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

### Trial information

#### Trial identification

Sponsor protocol code	CCMROne
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#### Additional study identifiers

ISRCTN number	ISRCTN14265371
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust & University of Cambridge
Sponsor organisation address	Hills Road, Cambridge, United Kingdom,
Public contact	Clinical Trials Regulatory Manager, Cambridge Clinical Trials Unit, +44 1223 348158, cctu@addenbrookes.nhs.uk
Scientific contact	Clinical Trials Regulatory Manager, Cambridge Clinical Trials Unit, +44 1223 348158, cctu@addenbrookes.nhs.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	01 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2019
Global end of trial reached?	Yes
Global end of trial date	17 May 2019
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective is to establish the safety and tolerability of bexarotene in the treatment of relapsing remitting multiple sclerosis.

Protection of trial subjects:

Adverse events were captured at every visit, and all adverse events were recorded on the case report form and reported in accordance with the trial protocol. Any serious adverse events were reviewed in a blinded fashion by the trial steering committee, which included the chief investigator, principal investigator from each site, statistician, Professor Robin Franklin (scientific advisor) or deputy, a thyroid advisor, a lipid advisor, and representatives from the funder and Sponsor.

Weekly (for the first month) then monthly fasting full blood count (FBC), thyroid function tests, liver function tests and lipid profile were performed and assessed by a clinician.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	17 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	56
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All participants were recruited from the UK.

### Pre-assignment

Screening details:

Potential participants were identified from multiple sclerosis clinics at the participating sites. Potential participants were also referred from other specialist centres. Full inclusion/exclusion criteria are outlined in the trial protocol.

### Pre-assignment period milestones

Number of subjects started	56
Number of subjects completed	52

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Excluded: Insufficient T2 lesions at MRI: 2
Reason: Number of subjects	Excluded: EDSS > 6.0: 2

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

A web-based randomisation system was used for randomisation and assigned a sequential patient number and a corresponding 'patient pack' number, used to select treatment to be dispensed (bexarotene or placebo), which was visually indistinguishable at the point of issue to the patient. MRI scans were labelled with two unique and random numbers (no patient identifiable information) to ensure the investigator analysing the scan remained blinded to treatment group.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Bexarotene (active)

Arm description:

Bexarotene 300mg/m<sup>2</sup> daily as a single dose with the evening meal, reduced, if poorly tolerated, to a minimum of 100mg/m<sup>2</sup>/day

Arm type	Experimental
Investigational medicinal product name	Bexarotene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The standard dose of bexarotene was initially 300mg/m<sup>2</sup> orally daily as a single dose with a meal, which may subsequently be titrated down to a minimum of 100 mg/m<sup>2</sup> depending on tolerability. The dose would be rounded down to the nearest available number of whole capsules. The dose was capped at a maximum of 10 capsules daily and body surface area calculated using the DuBois method.

<b>Arm title</b>	Placebo
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Arm description:

Placebo capsules to match active IMP

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules to match active IMP

<b>Number of subjects in period 1<sup>[1]</sup></b>	Bexarotene (active)	Placebo
Started	26	26
Completed	25	24
Not completed	1	2
Consent withdrawn by subject	1	-
Did not tolerate MRI (did not receive placebo)	-	1
Acute relapse (did not receive placebo)	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline period only includes participants who were randomised to receive treatment. 4 participants who had consented were excluded prior to randomisation.

## Baseline characteristics

### Reporting groups

Reporting group title	Bexarotene (active)
Reporting group description: Bexarotene 300mg/m2 daily as a single dose with the evening meal, reduced, if poorly tolerated, to a minimum of 100mg/m2/day	
Reporting group title	Placebo
Reporting group description: Placebo capsules to match active IMP	

Reporting group values	Bexarotene (active)	Placebo	Total
Number of subjects	26	26	52
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	26	26	52
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	15	15	30
Male	11	11	22

### Subject analysis sets

Subject analysis set title	Primary efficacy endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with follow-up data (as the metrics are change metrics so could not include those who declined follow-up)	
Subject analysis set title	Pre-defined exploratory endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with follow-up data (as the metrics are change metrics so could not include those who declined follow-up).	

Reporting group values	Primary efficacy endpoint	Pre-defined exploratory endpoint	
Number of subjects	49	49	
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)	49		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	Bexarotene (active)
Reporting group description: Bexarotene 300mg/m <sup>2</sup> daily as a single dose with the evening meal, reduced, if poorly tolerated, to a minimum of 100mg/m <sup>2</sup> /day	
Reporting group title	Placebo
Reporting group description: Placebo capsules to match active IMP	
Subject analysis set title	Primary efficacy endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with follow-up data (as the metrics are change metrics so could not include those who declined follow-up)	
Subject analysis set title	Pre-defined exploratory endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with follow-up data (as the metrics are change metrics so could not include those who declined follow-up).	

### Primary: Difference in mean within-patient change in lesional MTR in those lesions falling below the within-patient median ("submedian lesions")

End point title	Difference in mean within-patient change in lesional MTR in those lesions falling below the within-patient median ("submedian lesions")
End point description: Adjusted bexarotene-placebo difference (95% CI). Analysed by patient.	
End point type	Primary
End point timeframe: 6 month trial period (change between baseline (month 0) and month 6 scans)	

End point values	Bexarotene (active)	Placebo	Primary efficacy endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	24	49	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.25 (-0.13 to 0.63)	0.09 (-0.25 to 0.43)	0.16 (-0.39 to 0.71)	

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$ / $> 40$ years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$ / $> 4.0$ score). Data was analysed by patient.	



Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.554 <sup>[2]</sup>
Method	Multiple regression

Notes:

[1] - The patient-level change in mean lesional MTR between baseline and month 6 for those lesions whose MTR was below the within-patient median at baseline

[2] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in mean MTR of submedian lesions (defined by cohort-level median)

End point title	The change in mean MTR of submedian lesions (defined by cohort-level median)
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 923, Placebo = 662, Overall subject analysis set = 1585.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[3]</sup>	24 <sup>[4]</sup>	49 <sup>[5]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.35 (0.22 to 0.48)	-0.07 (-0.20 to 0.06)	0.30 (-0.18 to 0.78)	

Notes:

[3] - Number of lesions in group = 923

[4] - Number of lesions in group = 662

[5] - Number of lesions in group = 1585

### Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene = 923, Placebo = 662, Subject Analysis Set = 1585.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.223 <sup>[6]</sup>
Method	Multiple regression

Notes:

[6] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in mean MTR of supramedian lesions (defined by cohort-level median)

End point title	The change in mean MTR of supramedian lesions (defined by cohort-level median)
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 1023, Placebo = 562, Overall subject analysis set = 1585.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[7]</sup>	24 <sup>[8]</sup>	49 <sup>[9]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	-0.31 (-0.42 to -0.20)	-0.18 (-0.30 to -0.06)	-0.04 (-0.52 to 0.43)	

Notes:

[7] - Lesion numbers = 1023

[8] - Lesion numbers = 562

[9] - Lesion numbers = 1585

### Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.854 <sup>[10]</sup>
Method	Multiple regression

Notes:

[10] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in mean MTR of periventricular lesions

End point title	The change in mean MTR of periventricular lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 205, Placebo = 151, Overall subject analysis set = 356.

End point type	Other pre-specified
End point timeframe:	
6 months (baseline (month 0) to month 6)	

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[11]</sup>	24 <sup>[12]</sup>	49 <sup>[13]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	-0.31 (-0.54 to -0.08)	-0.18 (-0.39 to 0.03)	-0.02 (-0.58 to 0.55)	

Notes:

[11] - Number of lesions in group = 205

[12] - Number of lesions in group = 151

[13] - Number of lesions in group = 356

## Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.953 <sup>[14]</sup>
Method	Multiple regression

Notes:

[14] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in mean MTR of deep white matter lesions

End point title	The change in mean MTR of deep white matter lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 593, Placebo = 356, Overall subject analysis set = 949.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[15]</sup>	24 <sup>[16]</sup>	49 <sup>[17]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	-0.03 (-0.17 to 0.11)	0.01 (-0.13 to 0.15)	-0.06 (-0.56 to 0.44)	

Notes:

[15] - Number of lesions in group = 593

[16] - Number of lesions in group = 356

[17] - Number of lesions in group = 949

## Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.81 <sup>[18]</sup>
Method	Multiple regression

Notes:

[18] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in mean MTR of juxtacortical lesions

End point title	The change in mean MTR of juxtacortical lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 82, Placebo = 53, Overall subject analysis set = 135.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[19]</sup>	24 <sup>[20]</sup>	49 <sup>[21]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.09 (-0.28 to 0.46)	-0.16 (-0.74 to 0.42)	0.29 (-0.44 to 1.01)	

Notes:

[19] - Number of lesions in group = 82

[20] - Number of lesions in group = 53

[21] - Number of lesions in group = 135

## Statistical analyses

<b>Statistical analysis title</b>	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.441 [22]
Method	Multiple regression

Notes:

[22] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in mean MTR of leucocortical lesions

End point title	The change in mean MTR of leucocortical lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 649, Placebo = 389, Overall subject analysis set = 1038.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[23]</sup>	24 <sup>[24]</sup>	49 <sup>[25]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.00 (-0.16 to 0.16)	-0.02 (-0.18 to 0.14)	-0.04 (-0.54 to 0.46)	

Notes:

[23] - Number of lesions in group = 649

[24] - Number of lesions in group = 389

[25] - Number of lesions in group = 1038

## Statistical analyses

<b>Statistical analysis title</b>	Other pre-specified analysis
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**Statistical analysis description:**

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.864 <sup>[26]</sup>
Method	Multiple regression

Notes:

[26] - Statistical significance refers to  $p < 0.05$ .

**Other pre-specified: The change in mean MTR of cortical grey matter lesions**

End point title	The change in mean MTR of cortical grey matter lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 47, Placebo = 43, Overall subject analysis set = 90.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[27]</sup>	24 <sup>[28]</sup>	49 <sup>[29]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.68 (-0.05 to 1.41)	-0.35 (-1.26 to 0.56)	0.93 (0.12 to 1.75)	

Notes:

[27] - Number of lesions in group = 47

[28] - Number of lesions in group = 43

[29] - Number of lesions in group = 90

**Statistical analyses**

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
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Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03 <sup>[30]</sup>
Method	Multiple regression

Notes:

[30] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in mean MTR of deep grey matter lesions

End point title	The change in mean MTR of deep grey matter lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 7, Placebo = 9, Overall subject analysis set = 16.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[31]</sup>	24 <sup>[32]</sup>	49 <sup>[33]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.49 (-1.59 to 2.57)	-1.41 (-2.23 to -0.59)	1.93 (0.28 to 3.59)	

Notes:

[31] - Number of lesions in group = 7

[32] - Number of lesions in group = 9

[33] - Number of lesions in group = 16

### Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.027 <sup>[34]</sup>
Method	Multiple regression

Notes:

[34] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in mean MTR of mixed deep grey matter and white matter lesions

End point title	The change in mean MTR of mixed deep grey matter and white matter lesions
End point description: Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 217, Placebo = 158, Overall subject analysis set = 375.	
End point type	Other pre-specified
End point timeframe: 6 months (baseline (month 0) to month 6)	

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[35]</sup>	24 <sup>[36]</sup>	49 <sup>[37]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.10 (-0.14 to 0.34)	-0.24 (-0.46 to -0.02)	0.41 (-0.15 to 0.97)	

Notes:

[35] - Number of lesions in group = 217

[36] - Number of lesions in group = 158

[37] - Number of lesions in group = 375

## Statistical analyses

Statistical analysis title	Other pre-specified analysis
Statistical analysis description: Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$ / $> 40$ years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$ / $> 4.0$ score). Data was analysed by lesion using a nested model with patient random intercepts.	
Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.16 <sup>[38]</sup>
Method	Multiple regression

Notes:

[38] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in mean MTR of brainstem lesions

End point title	The change in mean MTR of brainstem lesions
End point description: Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 64, Placebo = 24, Overall subject analysis set = 88.	
End point type	Other pre-specified
End point timeframe: 6 months (baseline (month 0) to month 6)	



End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[39]</sup>	24 <sup>[40]</sup>	49 <sup>[41]</sup>	
Units: percentage units				
arithmetic mean (confidence interval 95%)	0.24 (-0.40 to 0.88)	-1.21 (-1.85 to -0.57)	1.75 (0.86 to 2.63)	

Notes:

[39] - Number of lesions in group = 64

[40] - Number of lesions in group = 24

[41] - Number of lesions in group = 88

## Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003 <sup>[42]</sup>
Method	Multiple regression

Notes:

[42] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in mean MTR of cerebellar lesions

End point title	The change in mean MTR of cerebellar lesions
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by lesion using a nested model with patient random intercepts. Lesion numbers: Bexarotene (active) = 82, Placebo = 41, Overall subject analysis set = 123.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[43]</sup>	24 <sup>[44]</sup>	49 <sup>[45]</sup>	
Units: percentage units				
arithmetic mean (confidence interval	0.04 (-0.45 to	-0.31 (-0.78 to	-0.03 (-0.79 to	

95%)	0.53)	0.16)	0.74)
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Notes:

[43] - Number of lesions in group = 82

[44] - Number of lesions in group = 41

[45] - Number of lesions in group = 123

## Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by lesion using a nested model with patient random intercepts.

Comparison groups	Placebo v Bexarotene (active)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.947 <sup>[46]</sup>
Method	Multiple regression

Notes:

[46] - Statistical significance refers to  $p < 0.05$ .

## Other pre-specified: The change in the P100 latency of the visual evoked potential for all eyes

End point title	The change in the P100 latency of the visual evoked potential for all eyes
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by eye using a nested model with patient random intercepts. Eye numbers: Bexarotene (active) = 42, Placebo = 44, Overall subject analysis set = 86.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[47]</sup>	24 <sup>[48]</sup>	49 <sup>[49]</sup>	
Units: ms				
arithmetic mean (confidence interval 95%)	-2.00 (-3.88 to -0.12)	0.70 (-0.69 to 2.09)	-2.85 (-5.75 to 0.05)	

Notes:

[47] - Number of eyes in group = 42

[48] - Number of eyes in group = 44

[49] - Number of eyes in group = 86

## Statistical analyses

<b>Statistical analysis title</b>	Other pre-specified analysis
Statistical analysis description: Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$ / $> 40$ years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$ / $> 4.0$ score). Data was analysed by eye using a nested model with patient random intercepts.	
Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.054 <sup>[50]</sup>
Method	Multiple regression
Notes: [50] - Statistical significance refers to $p < 0.05$ .	

### Other pre-specified: The change in the P100 latency of the visual evoked potential for eyes with baseline latency >118ms

End point title	The change in the P100 latency of the visual evoked potential for eyes with baseline latency >118ms
End point description: Adjusted bexarotene-placebo difference (95% CI)	
End point type	Other pre-specified
End point timeframe: 6 months (baseline (month 0) to month 6). Data was analysed by eye using a nested model with patient random intercepts. Eye numbers: Bexarotene (active) = 29, Placebo = 22, Overall subject analysis set = 51.	

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[51]</sup>	24 <sup>[52]</sup>	49 <sup>[53]</sup>	
Units: ms				
arithmetic mean (confidence interval 95%)	-3.46 (-5.93 to -0.99)	0.40 (-1.30 to 2.10)	-4.06 (-7.68 to -0.44)	

Notes:  
[51] - Number of eyes in group = 29  
[52] - Number of eyes in group = 22  
[53] - Number of eyes in group = 51

### Statistical analyses

<b>Statistical analysis title</b>	Other pre-specified analysis
Statistical analysis description: Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$ / $> 40$ years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$ / $> 4.0$ score). Data was analysed by eye using a nested model with patient random intercepts.	
Comparison groups	Bexarotene (active) v Placebo

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028 <sup>[54]</sup>
Method	Multiple regression

Notes:

[54] - Statistical significance refers to  $p < 0.05$ .

### Other pre-specified: The change in the P100 latency of the visual evoked potential for eyes with baseline latency >118ms and no history of optic neuritis in previous 5 years

End point title	The change in the P100 latency of the visual evoked potential for eyes with baseline latency >118ms and no history of optic neuritis in previous 5 years
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End point description:

Adjusted bexarotene-placebo difference (95% CI). Data was analysed by eye using a nested model with patient random intercepts. Eye numbers: Bexarotene (active) = 26, Placebo = 17, Overall subject analysis set = 43.

End point type	Other pre-specified
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End point timeframe:

6 months (baseline (month 0) to month 6)

End point values	Bexarotene (active)	Placebo	Pre-defined exploratory endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25 <sup>[55]</sup>	24 <sup>[56]</sup>	49 <sup>[57]</sup>	
Units: ms				
arithmetic mean (confidence interval 95%)	-3.87 (-6.55 to -1.19)	0.08 (-1.88 to 2.04)	-4.75 (-8.80 to -0.71)	

Notes:

[55] - Number of eyes in group = 26

[56] - Number of eyes in group = 17

[57] - Number of eyes in group = 43

### Statistical analyses

Statistical analysis title	Other pre-specified analysis
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Statistical analysis description:

Treatment effect was estimated using multiple regression of the outcome measure on a group indicator with the following prespecified trial covariates: the baseline value of the outcome measure and the four binary minimisation factors: age ( $\leq 40$  /  $> 40$  years), gender, trial centre/scanner (London/Edinburgh) and EDSS ( $\leq 4.0$  /  $> 4.0$  score). Data was analysed by eye using a nested model with patient random intercepts.

Comparison groups	Bexarotene (active) v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.032 <sup>[58]</sup>
Method	Multiple regression

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Notes:

[58] - Statistical significance refers to  $p < 0.05$ .

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the point of informed consent (screening) to end of trial participation (month 9)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

Reporting group title	Bexarotene (active)
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Reporting group description:

Bexarotene 300mg/m2 daily as a single dose with the evening meal, reduced, if poorly tolerated, to a minimum of 100mg/m2/day

Reporting group title	Placebo
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Reporting group description:

Placebo capsules to match active IMP

Serious adverse events	Bexarotene (active)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bexarotene (active)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	17 / 24 (70.83%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 6	4 / 24 (16.67%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Shortness of breath subjects affected / exposed occurrences (all)  Sore throat subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1  0 / 26 (0.00%) 0  1 / 26 (3.85%) 1	1 / 24 (4.17%) 1  1 / 24 (4.17%) 1  1 / 24 (4.17%) 1	
Psychiatric disorders Low mood subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Investigations Transaminitis subjects affected / exposed occurrences (all)  Weight loss subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3  1 / 26 (3.85%) 1	0 / 24 (0.00%) 0  0 / 24 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Multiple sclerosis relapse subjects affected / exposed occurrences (all)  Multiple sclerosis pseudo relapse subjects affected / exposed occurrences (all)  Lhermitte's sign	14 / 26 (53.85%) 14  1 / 26 (3.85%) 1  1 / 26 (3.85%) 1	8 / 24 (33.33%) 8  0 / 24 (0.00%) 0  4 / 24 (16.67%) 4	

subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cerebellar infarction			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Neuropathic pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Muscle spasticity aggravated			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Memory disturbance			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 26 (38.46%)	0 / 24 (0.00%)	
occurrences (all)	10	0	
Lymphopenia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Eye disorders			
Dry eyes			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dry lips			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Ulceration of mouth			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Nausea			



subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5	0 / 24 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	4 / 24 (16.67%) 4	
Constipation subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 24 (0.00%) 0	
Epigastric pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	13 / 26 (50.00%) 13	1 / 24 (4.17%) 1	
Pruritis subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 7	0 / 24 (0.00%) 0	
Skin desquamation subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5	0 / 24 (0.00%) 0	
Dry skin subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	0 / 24 (0.00%) 0	
Acne subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Alopecia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Facial flushing subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 24 (8.33%) 2	
Renal and urinary disorders			
Nocturia			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 24 (0.00%) 0	
Urinary frequency subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 24 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Stiffness joints subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 24 (4.17%) 1	
Myalgia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Infections and infestations			
URTI subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 24 (4.17%) 1	
LRTI subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
UTI subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 24 (4.17%) 1	
Shingles subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 24 (4.17%) 1	
Ear infection subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 24 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 24 (4.17%) 1	
Coryzal symptoms subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	4 / 24 (16.67%) 4	
Metabolism and nutrition disorders			

Hypertriglyceridaemia			
subjects affected / exposed	24 / 26 (92.31%)	0 / 24 (0.00%)	
occurrences (all)	24	0	
Secondary hypothyroidism			
subjects affected / exposed	26 / 26 (100.00%)	0 / 24 (0.00%)	
occurrences (all)	26	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2016	<ol style="list-style-type: none"><li>1. The changes outlined to study title, eligibility criteria, study procedures (including MRI) and safety information have been carried out to reflect:<ol style="list-style-type: none"><li>a. Lack of scientific justification to exclude participants on other MS first-line (ABN category 1) disease-modifying therapies</li><li>b. Renewed UK guidance for alcohol intake in adults</li><li>c. Revised SmPC for Bexarotene</li><li>d. MTR outcome measure is now possible to standardise between sites</li><li>e. Local nursing practices</li></ol></li><li>2. Owing to a period of temporary closure at the Royal Free Pharmacy Manufacturing Unit, manufacture (i.e. over-encapsulation of Bexarotene and production of matched-placebo) may require outsourcing and the protocol has been amended to reflect this. The Royal Free Pharmacy Manufacturing Unit will, however, remain responsible for QP batch certification of the finished product.</li><li>3. To reduce the number of study visits for participants (and thus burden of the research) by revising recruitment procedures to invite participants to attend their screening visit in a fasted state for purpose of blood sample collection.</li><li>4. Typographical errors in the protocol have been rectified.</li></ol>
22 May 2017	<p>Changes to the patient eligibility criteria, following further advice from the Trial Management Group:</p> <ol style="list-style-type: none"><li>1. Patient age requirement now 18-50 (previously 30-50).</li><li>2. Kurtzke EDSS requirement now 0.0-6.0 (previously 3.0-6.0).</li><li>3. Removed previous requirement of 'at least one relapse in the two years prior to screening'.</li><li>4. Changed definition of RSI in Section 11.1.6.</li></ol>
17 January 2018	<ol style="list-style-type: none"><li>1. Changes to the patient eligibility criteria, following the first meeting of the Trial Steering Committee.</li><li>2. To specify that the review of a patient's screening visit results, and the subsequent documentation of the patient's eligibility to enter the trial, can be performed by 'an Investigator', rather than only the 'Chief or Principal Investigator'.</li><li>3. To specify that the blood samples for measuring peripheral immune markers will only be taken at the Cambridge site, not at the Edinburgh participating site.</li><li>4. To introduce an EDSS assessment at the Month 9 trial visit (Visit 11).</li><li>5. Definition of 'weekly' and 'monthly' in trial visit scheduling.</li><li>6. Minor text changes to cover: frequency of TSC meetings; frequency of meetings between Chief Investigator and trial Lipid Advisor; storage freezer temperature settings; correction of typographical errors.</li></ol>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

None

Notes: