



Clinical trial results:

Oxcarbazepine as a neuroprotective agent in MS: phase 2a trial

Summary

EudraCT number	2013-002419-87
Trial protocol	GB
Global end of trial date	26 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 July 2019
First version publication date	03 July 2019
Summary attachment (see zip file)	Adverse events information (Adverse events information.xlsx)

Trial information

Trial identification

Sponsor protocol code	008722
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02104661
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	JMRO 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Mays Jawad, Barts Health NHS Trust, 0044 02078827260, research.governance@qmul.ac.uk
Scientific contact	Mays Jawad, Barts Health NHS Trust, 0044 02078827260, research.governance@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	12 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2018
Global end of trial reached?	Yes
Global end of trial date	26 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does oxcarbazepine protect people with multiple sclerosis (PwMS) from nerve loss? When we compare PwMS who take oxcarbazepine for one year to PwMS who take placebo, is the level of neurofilament light (NFL), a marker of nerve loss, in the CSF significantly reduced?

Protection of trial subjects:

Cerebrospinal fluid (CSF) Neurofilament light chain (NFL) level measurement require participants to undergo a Lumbar Puncture procedure Some people with multiple sclerosis (MS) will accept to have four lumbar punctures (LP) to measure NFL in order to have the chance of reducing the risk of permanent nerve loss. We have run a online pool asking people opinion about having LP in a trial for a neuroprotective drug in our site msres.org and had a positive outcome. We will have a youtube video showing what a LP with atraumatic needle is like for those who want to see it. Currently, the markers of neurodegeneration in the serum are not reliable or validated. The neuroprotective drug we are testing, oxcarbazepine, is a sodium channel blocker, a group of drugs that showed promise but not yet definite results in MS. It is also a widely used drug in Neurology, licensed for epilepsy. The dose we will use is lower than for epilepsy, which reduces the occurrence of dose dependent side effects. Adverse events side effects are monitored at every visit and safety bloods every three months. We will recruit people who are under licensed disease modifying drugs for MS, but who have raised levels of neurofilament in the CSF, a marker that there is continuous neurodegeneration. Even if we and the participants are blinded, it is possible to break the code in case of serious adverse events. Also, it is possible to unblind because of side effects and we have chosen not to have blinded independent assessors. The justification is that our primary outcome measures is objective and independent of the observer/analyst. Participants will be asked to give up to 60mls of blood for safety and tertiary research outcomes. Patients will asked to consent. A Data Safety Monitoring Committee will be put in place to independently monitor the safety of the patients and the ongoing values of the trial. The DSMC will meet after the first SAE or 1 month after 50% of participants have entered the Study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2014
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants will be assessed for inclusion following informed consent. After their initial screening they will undergo a lumbar puncture for assessment of baseline Cerebrospinal fluid Neurofilament light (CSF NFL) levels. Only participants with raised CSF NFL levels ($> 0.380\text{ng/mL}$) will be eligible for randomization.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental: OxCarbazepine Treatment

Arm description:

Treated for 48 weeks with OxCarbazepine 600mg (2 X 150mg tablets twice a day) alongside current DMDs

Arm type	Experimental
Investigational medicinal product name	OxCarbazepine Treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

300 mg twice a day

Arm title	Placebo Comparator: OxCarbazepine Placebo
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Arm description:

Treated for 48 weeks with OxCarbazepine Placebo (2 tablets twice a day) alongside current DMDs

Arm type	Placebo
Investigational medicinal product name	OxCarbazepine Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

tablets

Number of subjects in period 1	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo
Started	16	14
Completed	15	14
Not completed	1	0
Physician decision	1	-

Baseline characteristics

Reporting groups

Reporting group title	Experimental: OxCarbazepine Treatment
Reporting group description: Treated for 48 weeks with OxCarbazepine 600mg (2 X 150mg tablets twice a day) alongside current DMDs	
Reporting group title	Placebo Comparator: OxCarbazepine Placebo
Reporting group description: Treated for 48 weeks with OxCarbazepine Placebo (2 tablets twice a day) alongside current DMDs	

Reporting group values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo	Total
Number of subjects	16	14	30
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)	16	14	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.57	49.37	
standard deviation	± 9.61	± 6.18	-
Gender categorical Units: Subjects			
Female	11	5	16
Male	5	9	14

End points

End points reporting groups

Reporting group title	Experimental: OxCarbazepine Treatment
Reporting group description: Treated for 48 weeks with OxCarbazepine 600mg (2 X 150mg tablets twice a day) alongside current DMDs	
Reporting group title	Placebo Comparator: OxCarbazepine Placebo
Reporting group description: Treated for 48 weeks with OxCarbazepine Placebo (2 tablets twice a day) alongside current DMDs	

Primary: Primary: Mean cerebro-spinal fluid (CSF) neurofilament light chain (NFL) levels from baseline to 48 weeks between the active and placebo treated arms.

End point title	Primary: Mean cerebro-spinal fluid (CSF) neurofilament light chain (NFL) levels from baseline to 48 weeks between the active and placebo treated arms.
End point description:	
End point type	Primary
End point timeframe: from baseline to 48 weeks	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: pg / mL				
arithmetic mean (standard deviation)	408.65 (± 125.94)	449.22 (± 164.88)		

Statistical analyses

Statistical analysis title	Primary Outcome: NFL CSF levels
Statistical analysis description: The primary analysis for this outcome will estimate the adjusted Active-Placebo difference in mean NFL at 48 weeks use the following simplified schematic for a multiple linear regression: $NFL_{48w} = \text{Alpha} + \text{Beta.Active} + \text{Gamma1NFL baseline} + \text{Gamma2binaryEDSS baseline}$. Minimisation variables (both binary): Baseline CSF NFL level (< 0.5ng/mL , > 0.5ng/mL), Baseline Expanded Disability Status Scale (EDSS < 5.0 , > 5.0)	
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.751
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-15.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-112.46
upper limit	82.18
Variability estimate	Standard error of the mean
Dispersion value	47.26

Secondary: Secondary: Mean Expanded Disability Status Scale (EDSS) score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean Expanded Disability Status Scale (EDSS) score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: score				
arithmetic mean (standard deviation)	4.87 (\pm 1.16)	5.54 (\pm 1.01)		

Statistical analyses

Statistical analysis title	Secondary Outcome: EDSS
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Secondary: Mean "Twelve Item Multiple Sclerosis Walking Scale" (MSWS-12 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean "Twelve Item Multiple Sclerosis Walking Scale" (MSWS-12 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: score				
arithmetic mean (standard deviation)	52.70 (± 27.09)	73.44 (± 22.01)		

Statistical analyses

Statistical analysis title	Secondary Outcome: MSWS-12 v2
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-12.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.14
upper limit	-0.49
Variability estimate	Standard error of the mean
Dispersion value	5.96

Secondary: Secondary: Mean "Multiple Sclerosis Physical Impact Scale" (MSIS-29 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean "Multiple Sclerosis Physical Impact Scale" (MSIS-29 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: score				
arithmetic mean (standard deviation)	41.67 (± 21.46)	52.38 (± 18.43)		

Statistical analyses

Statistical analysis title	Secondary Outcome: MSIS-29 v2 Physical
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.82
upper limit	9.88
Variability estimate	Standard error of the mean
Dispersion value	5

Secondary: Secondary: Mean "Multiple Sclerosis Psychological Impact Scale" (MSIS-29 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean "Multiple Sclerosis Psychological Impact Scale" (MSIS-29 v2) questionnaire score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: score				
arithmetic mean (standard deviation)	36.54 (± 21.54)	35.19 (± 17.30)		

Statistical analyses

Statistical analysis title	Secondary Outcome: MSIS-29 v2 Psychological
Comparison groups	Placebo Comparator: OxCarbazepine Placebo v Experimental: OxCarbazepine Treatment

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.692
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.46
upper limit	14.01
Variability estimate	Standard error of the mean
Dispersion value	5.67

Secondary: Secondary: Mean Fatigue score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean Fatigue score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: score				
arithmetic mean (standard deviation)	54.80 (± 22.40)	63.93 (± 13.06)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fatigue score
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.01
upper limit	13.29
Variability estimate	Standard error of the mean
Dispersion value	7.07

Secondary: Secondary: Mean Pain score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean Pain score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: score				
arithmetic mean (standard deviation)	26.01 (± 25.75)	35.52 (± 29.91)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Pain score
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-12.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.47
upper limit	8.18
Variability estimate	Standard error of the mean
Dispersion value	9.85

Secondary: Secondary: Mean Symbol Digit Modalities Test (SDMT) score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean Symbol Digit Modalities Test (SDMT) score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: score				
arithmetic mean (standard deviation)	42.67 (± 19.82)	42.07 (± 11.03)		

Statistical analyses

Statistical analysis title	Secondary Outcome: SDMT
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.838
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.83
upper limit	4.77
Variability estimate	Standard error of the mean
Dispersion value	2.57

Secondary: Secondary: Mean Sloan Chart score from baseline to 48 weeks between the active and placebo treated arms

End point title	Secondary: Mean Sloan Chart score from baseline to 48 weeks between the active and placebo treated arms
End point description:	
End point type	Secondary
End point timeframe:	
48 weeks from baseline	

End point values	Experimental: OxCarbazepine Treatment	Placebo Comparator: OxCarbazepine Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: score				
arithmetic mean (standard deviation)	8.41 (± 5.85)	16.53 (± 20.99)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Sloan Chart
Comparison groups	Experimental: OxCarbazepine Treatment v Placebo Comparator: OxCarbazepine Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	ANCOVA
Parameter estimate	baseline adjusted mean difference
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.51
upper limit	3.31
Variability estimate	Standard error of the mean
Dispersion value	5.71

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

between baseline and 48 weeks

Adverse event reporting additional description:

Adverse events were recorded for all subjects randomised

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14
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Reporting groups

Reporting group title	Experimental: OxCarbazepine Treatment
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Reporting group description:

Treated for 48 weeks with OxCarbazepine 600mg (2 X 150mg tablets twice a day) alongside current DMDs

Reporting group title	Placebo comparator - OxCarbazepine Placebo
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Reporting group description:

Treated for 48 weeks with OxCarbazepine Placebo (2 tablets twice a day) alongside current DMDs

Serious adverse events	Experimental: OxCarbazepine Treatment	Placebo comparator - OxCarbazepine Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Experimental: OxCarbazepine Treatment	Placebo comparator - OxCarbazepine Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The system has an error (see EMA call ref: SD-277614) that does not allow us to add the non serious adverse events. We have added a document detailing the adverse events for this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2015	<p>The purpose of this substantial amendment is to make administrative changes, clarifications and corrections.</p> <p>The sections which have been reviewed include the inclusion/exclusion criteria, the criteria for premature withdrawal and the prohibited concomitant medications.</p> <p>Summary of revisions:</p> <ol style="list-style-type: none">1 The study title in the study summary and the first protocol page have been made consistent.2. The unit used for cerebral spinal fluid neurofilament (CSF NFL) has been corrected from pg/mL to ng/mL.3. Numbering has been introduced to replace bullet points in sections 3.3 and 3.4.4. Protocol section 3.3: in inclusion criterion 3 the CSF NFL threshold for eligibility has been lowered from 0.690 ng/mL to 0.380 ng/mL. The rationale for this is detailed in Section 1.1 'Background'. It was observed on the screened participants that the values of CSF NFL in people with early SPMS who are on effective disease-modifying therapies are lower than the published results; this has only come to light since starting this study and will increase the number of subjects eligible for the study.6. Protocol section 4.8: Use of induction therapies as a DMD for MS has been clarified.7. Two new exclusion criteria have been introduced: Exclusion criterion 2 to exclude participants with a diagnosis of primary progressive or progressive relapsing MS to be consistent with the study summary and exclusion criterion 11 to exclude participants who have received OxCbz or Cbz in the previous 12 weeks from baseline.8. The use of sodium or calcium channel blockers has been removed from sections 3.3 'Exclusion criteria', 4.8 'Prior and concomitant medications' and 4.10 'Medications to control MS symptoms'. This has been removed because sodium and calcium channel blockers do not interfere with the mechanism of Oxcarbazepine. The use of induction DMDs has been clarified in section 4.8.9 DMD discontinuation has been introduced as an additional criteria for premature withdrawal in section 3.4 to be c

21 October 2016	<p>The purpose of this substantial amendment is to make administrative changes, clarifications and corrections.</p> <p>Various protocol sections were reviewed, including: Study summary, Study design, Study population, Inclusion/Exclusion Criteria, Investigational Medicinal Product, Schedule of assessments table, Statistical considerations and Data handling and record keeping.</p> <p>Summary of revisions:</p> <ol style="list-style-type: none"> 1. Exclusion criteria 1 has been updated to include details of adequate methods of contraception and to clarify the requirements for participants in same sex relationships and those who are not sexually active. 2. Exclusion criteria 3 has been updated to clarify the use of pulse intravenous or oral steroids for MS relapses 3. Inclusion criterion 2 in Protocol Section 3.3 has been updated to allow for the temporary interruption of disease modifying drug at the discretion of the Investigator. For consistency, this change was also applied to criterion for premature withdrawal n.8 in section 3.4 and to section 4.8 'Prior and concomitant medications'. 4. The number of participants required to be randomised in the study has been reduced to 30 (15 per arm). The number of participants required to complete the study has been reduced to 26. This decision is substantiated by a review of the power calculation for the study by the study statistician and CI. The data collected from the baseline sample was used to assess that the sample size could safely be reduced. 5. The level of CSF NFL level reduction for the detection of a significant treatment effect has been updated to 30%. 6. The use of the Simplified Investigational Medicinal Product Dossier in the study has been clarified. References to the SIMPD have been made consistent throughout all protocol sections. 5. Administrative corrections were made to the IMP section 6. The information included in the separate sections of the IMP label has been clarified. 7. To follow is a list of the changes made
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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.

The system has an error (see EMA call ref: SD-277614) that does not allow us to add the non serious adverse events. We have added a document detailing the adverse events for this trial.

Notes: