Clinical trial results:
A phase II double-blind, randomised, placebo-controlled trial of neuroprotection with phenytoin in acute optic neuritis

Summary

EudraCT number	2011-003475-11
Trial protocol	GB
Global end of trial date	06 December 2014

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	UCL/11/0083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01451593
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom,
Public contact	CTIMPs , University College London (UCL), 0044 020 7679 6802, ctimps@ucl.ac.uk
Scientific contact	CTIMPs, University College London (UCL), 0044 020 7679 6802, ctimps@ucl.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	18 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2014
Global end of trial reached?	Yes
Global end of trial date	06 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In optic neuritis, there is inflammation of the optic nerve, which carries visual information from the eye into the brain. People with optic neuritis lose vision in the eye affected by the disorder, and vision may not recover fully.
Current therapy for optic neuritis can lead to a faster recovery of vision, but does not improve the extent to which vision would recover eventually without treatment. Recent work suggests that loss of vision is due to damage to the nerve fibres in the optic nerve (which is accompanied by damage to the nerve fibres in the retina), that the damage is secondary to a buildup of sodium in these fibres, and that it can be prevented by blocking the entry of sodium into them.
In this clinical trial, the principal objective is to assess whether immediate and sustained blockade of the entry of sodium into nerve fibres with the drug phenytoin protects nerve fibres in the retina and optic nerve from degeneration after an attack of optic neuritis.

Protection of trial subjects:

Full blood count, urea, electrolytes, liver function tests were taken at the screening visit and each subsequent visit to ensure safety. Urine pregnancy test and ECG were also performed at the screening visit to ensure there was no contraindication to phenytoin. Aqua porin 4 antibodies were also taken at the the screening visit and patients found to be seropositive withdrawn from the trial. Participants were assessed clinically by a treating physician at 1, 3 and 6 months from baseline to assess safety

Background therapy:

Concurrent treatment with glatiramer acetate or interferon beta was permitted and corticosteroids for acute optic neuritis could be given at the treating physician’s discretion (all participants were offered equivalent regimens of methylprednisolone, either 1 g intravenously daily for 3 days, or 500 mg orally daily for 5 days).

Evidence for comparator:

Corticosteroids hasten recovery after optic neuritis without affecting the final prognosis for recovery. Also previous studies show that corticosteroids do not prevent atrophy of the RNFL or optic nerve, nor visual recovery after optic neuritis and immunomodulation has so far had limited effects on progressive disability. Currently there are no treatments that affect outcome after optic neuritis or other MS relapses. Hence, neuroprotection for both processes contributing to axonal loss and disability remains a key unmet need in optic neuritis and MS.
The anterior visual system has many advantages for testing neuroprotection in MS: acute demyelinating optic neuritis (AON) is a common and often presenting manifes-tation of MS; the inflammatory optic nerve lesion is comparable to plaques found elsewhere in the central nervous system; and the visual system can be studied using clinical, electrophysiological and imaging techniques. In addition, the optic nerve le-sion leads to retrograde degeneration of the retinal nerve fibre layer (RNFL), a relatively pure compartment of unmyelinated axons whose thickness can be measured sensitively and non-invasively using optical coherence tomography (OCT). Therefore, the RNFL thickness provides a plausible biomarker of axonal loss. Reduction of RNFL thickness also corresponds with visual loss in AON and with changes of disability in MS, suggesting that it may provide information on treatment response that is also clinically relevant.

Actual start date of recruitment	03 October 2011
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: 92
Worldwide total number of subjects	92
EEA total number of subjects	92

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)	92
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between Feb 3, 2012, and May 22, 2014, and we performed the final assessments in December, 2014
Patients were recruited from one two trial centres in London and Sheffield, UK, or were referred there from a UK network of patient identification centres,

Pre-assignment

Screening details:

Patients were eligible if they were aged 18–60 years, had a clinical diagnosis of unilateral acute demyelinating optic neuritis with no alternative pathological abnormalities on OCT at presentation), visual acuity of 6/9 or worse, and an interval of 14 days or less between onset of vision loss and randomisation

Pre-assignment period milestones

Number of subjects started	92
Number of subjects completed	86

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 6

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, Monitor, Assessor

Blinding implementation details:

Participants were randomly assigned (1:1) to phenytoin or placebo via an online randomisation service. Participants were allocated a randomisation code by the treating physician, which was matched to a confidential treatment list by the study pharmacist to assign participants either to phenytoin or placebo (which were identical in appearance). Only the pharmacist was aware of treatment allocation. Treating and assessing physicians and participants were masked to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

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

Dosage and administration details:

articipants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal

doses (each rounded up to the nearest 50 mg) for a period of 3 days
A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

Arm title	Placebo

Arm description:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

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

Dosage and administration details:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

Number of subjects in period 1[1]	Active	Placebo
Started	42	44
Completed	39	42
Not completed	3	2
Lost to follow-up	3	2

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: 92 patients were initially enrolled into the trial but 6 patients were subsequently withdrawn after entry into the trial due to alternative diagnoses - this is the reason for this discrepancy

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.	
Reporting group title	Placebo
Reporting group description:	
Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient	

Reporting group values	Active	Placebo	Total
Number of subjects	42	44	86
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	33	35	
standard deviation	± 8.2	± 9.1	-
Gender categorical			
Units: Subjects			
Female	31	32	63
Male	11	12	23

End points

End points reporting groups

Reporting group title	Active

Reporting group description:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

Reporting group title	Placebo

Reporting group description:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

Primary: Active-placebo difference in mean 6 month RNFL thickness adjusted for the baseline RNFL thickness of the unaffected eye

End point title	Active-placebo difference in mean 6 month RNFL thickness adjusted for the baseline RNFL thickness of the unaffected eye

End point description:

High resolution spectral domain OCT images (Spectralis, software version 5.4B, Heidelberg Engineering, Heidelberg, Germany) were acquired at baseline and 6 months using identical protocols at both sites. RNFL measurements used a 3·45 mm diameter circle scan.

End point type	Primary

End point timeframe:

Mean RNFL thickness was measured at baseline and at 6 months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	42		
Units: microns				
arithmetic mean (standard deviation)	81.46 (± 16.27)	74.29 (± 15.14)		

Statistical analyses

Statistical analysis title	Primary outcome analysis

Statistical analysis description:

We used an ANCOVA analysis method, using multiple linear regression of the 6-month RNFL of the affected eye on a trial arm indicator with the following prespecified covariates: baseline RNFL thickness in the fellow eye, centre (binary), days between onset and baseline assessment, and whether the participant was prescribed corticosteroids at the time of baseline assessment (no vs 1–5 days before assessment vs 6–30 days before assessment).

Comparison groups	Active v Placebo

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - The trial was powered to detect a treatment effect of 50% at a 5% significance level at 80% power while allowing for a 20% combined rate of loss to follow-up and non-adherence.
[2] - Statistical significance, where referred to, indicates a p value of less than 0·05, and all p values refer to two-tailed tests. When regression residuals showed signs of non- normality or heteroscedasticity, we checked p values using a permutation te

Secondary: Active-placebo difference in mean 6 month logMAR visual acuity adjusted for the baseline measurement in the unaffected eye

End point title	Active-placebo difference in mean 6 month logMAR visual acuity adjusted for the baseline measurement in the unaffected eye

End point description:

Best corrected high-contrast logMAR visual acuity was measured using retro-illuminated Early Treatment Diabetic Retinopathy Study charts at 4 m. When no letters could be correctly identified, a score of 1·7 was assigned by the masked researcher.

End point type	Secondary

End point timeframe:

Best corrected logMAR visual acuity was measured at baseline and 6 months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	42		
Units: logMAR				
arithmetic mean (standard deviation)	0.09 (± 0.4)	0.04 (± 0.18)		

Statistical analyses

Statistical analysis title	Secondary endpoints

Statistical analysis description:

We analysed secondary outcomes in the same way as the primary outcome measure using the corresponding baseline fellow-eye value of the outcome and the same prespecified covariates.

Comparison groups	Placebo v Active
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - The trial was powered to detect a treatment effect of 50% at a 5% significance level at 80% power for the primary outcome measure while allowing for a 20% combined rate of loss to follow-up and non-adherence. The trial was not powered to detect treatment effects in the secondary outcome measures

Secondary: Active-placebo difference in mean 6 month low contrast letter score (2.5%) adjusted for the baseline measurement in the unaffected eye

End point title	Active-placebo difference in mean 6 month low contrast letter score (2.5%) adjusted for the baseline measurement in the unaffected eye

End point description:

low-contrast letter scores were measured at baseline and 6 months using retro- illuminated 1·25% and 2·5% Sloan charts (Precision Vision, La Salle, IL, USA) using best refractive correction for each eye at 2 m.

End point type	Secondary

End point timeframe:

Low contrast letters scores at both 1.25% and 2.5% were measured at baseline and 6 months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	42		
Units: low contrast letter score				
arithmetic mean (standard deviation)	19.69 (± 13.8)	17.55 (± 14.19)		

Statistical analyses

Statistical analysis title	Secondary endpoints

Statistical analysis description:

We analysed secondary outcomes in the same way as the primary outcome measure using the corresponding baseline fellow-eye value of the outcome and the same prespecified covariates.

Comparison groups	Active v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Active-placebo difference in mean 6 month FM-Hue 100 error score adjusted for the baseline measurement in the unaffected eye

End point title	Active-placebo difference in mean 6 month FM-Hue 100 error score adjusted for the baseline measurement in the unaffected eye

End point description:

Colour vision was assessed by masked researchers using the Farnsworth-Munsell 100 hue test and recorded as the total error score. This test was assessed under standard daylight conditions using daylight linear full-spectrum bulbs with a colour temperature of 6500 K in participants with a logMAR visual acuity better than 1·0.

End point type	Secondary

End point timeframe:

FM-Huee 100 error score was measured at baseline and 6 months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	42		
Units: FM-Hue 100 error score				
arithmetic mean (standard deviation)	181.28 (± 223.79)	195.24 (± 212.61)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: active-placebo difference in mean total macular volume adjusted for the baseline measurement in the unaffected eye

End point title	active-placebo difference in mean total macular volume adjusted for the baseline measurement in the unaffected eye

End point description:

A fast macular volume scan (20 x20° field, 25 horizontal B scans, ART 9) was performed using a Heidelberg Spectralis machine. Scans were excluded if they had a signal strength of <25 or violated international consensus quality control criteria.

End point type	Secondary

End point timeframe:

Macular volume was measured at baseline and 6 months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	42		
Units: mm3				
arithmetic mean (standard deviation)	8.25 (± 0.45)	8.07 (± 0.42)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

Secondary outcomes were analysed in a similar way to the primary outcome measure, with the corresponding baseline fellow-eye value and the same pre-specified covariates.

Comparison groups	Active v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded for the 6 month follow up period	
Adverse event reporting additional description:	
Adverse events were analysed in all randomised patients including those lost to follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Active
Reporting group description:	
Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.	
Reporting group title	Placebo
Reporting group description:	
Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient	

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 42 (11.90%)	2 / 44 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Incidental finding of dilated superior opthalmic vein seen on MRI			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Congenital malformation	Additional description: Microtia following unplanned conception after randomisation		
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe rash			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 42 (80.95%)	40 / 44 (90.91%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 42 (42.86%)	15 / 44 (34.09%)	
occurrences (all)	18	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 42 (7.14%)	17 / 44 (38.64%)	
occurrences (all)	3	17	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5	7 / 44 (15.91%) 7	
Skin and subcutaneous tissue disorders rash subjects affected / exposed occurrences (all)	 8 / 42 (19.05%) 8	 1 / 44 (2.27%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2011	This amendment was sent as a part of the changes MHRA mentioned in the grounds of Non acceptance. New version of the protocol was submitted to the MHRA.
24 October 2011	This amendment was done as part of the changes required as per the provisional opinion from the ethics committee. Main study and sub study patient information sheets were modified and sent to the Ethics committee for approvals.
02 July 2012	Changes were done to Protocol and Patient Information Sheet. Protocol changes include minor changes to the inclusion criteria, schematic diagram of overall trial design, and minor treatment procedures.
09 November 2012	This amendment was done to reflect the change in the IMP supplier used in the Trial. The license was transferred from Pfizer to Flynn Pharma. This is administrative change and hence the protocol and IMPD were updated and notified to the MHRA
05 June 2013	The maintenance dose of the study drug was increased from 4mg/kg to 6mg/kg. The protocol has been updated to reflect the change and was notified to the regulatory bodies in the UK.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported