Clinical trial results:
A randomised double-blind placebo-controlled trial of the safety and efficacy of ethosuximide 250mg capsules for the management of chemotherapy-induced painful peripheral neuropathy.

Summary

EudraCT number	2008-004499-38
Trial protocol	GB
Global end of trial date	09 July 2014

Results information

Result version number	v1 (current)
This version publication date	28 September 2016
First version publication date	28 September 2016

Trial information

Trial identification

Sponsor protocol code	CCR 3116

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Royal Marsden NHS Foundation Trust
Sponsor organisation address	Sutton, London, United Kingdom, Sm25pt
Public contact	Clinical R&D Office, Royal Marsden NHS Foundation Trust, 0044 2086613903,
Scientific contact	Clinical R&D Office, Chief Investigator, 0044 20878082856,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2014
Global end of trial reached?	Yes
Global end of trial date	09 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

A randomised double-blind placebo-controlled trial of the safety and efficacy of ethosuximide for the management of chemotherapy-induced painful peripheral neuropathy.

Primary outcome measure will be the reduction in average pain intensity from baseline to end-point as measure on a 0-10 numerical rating scale.

Protection of trial subjects:

Trial was conducted in accordance with protocol. No additional measures were taken.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	12
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult cancer patients with chemotherapy-induced painful peripheral neuropathy were eligible for consideration of entry to the CIN-E study. Inclusion criteria include: pain severity of ≥4/10 on a numerical rating scale, and pain duration of ≥4 weeks. Recruitment continued from March 2011 to July 2014.

Pre-assignment

Screening details:

No screen failures are reported.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ethosuximide

Arm description:

Patients randomised to receive Ethosuximide

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

Dosage and administration details:

250mg oral capsule. Dosage titrated to effect according to following schedule-

Week 1- 250mg (250mg o.d.)
Week 2- 500mg (250mg b.d.)
Week 3- 750mg (250mg mane, 500mg nocte)
Week 4- 1000mg (500mg b.d.)
Week 5- 1500mg (750mg b.d.)
Week 6- 1500mg (750mg b.d.)

Arm title	Placebo

Arm description:

Patients randomised to receive placebo

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:

The placebo was administered under an identical schedule to the active IMP, i.e. 250mg capsules titrated over 6 weeks.

Number of subjects in period 1	Ethosuximide	Placebo
Started	7	8
Completed	0	7
Not completed	7	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	5	1
Unsatisfactory response	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ethosuximide
Reporting group description:	
Patients randomised to receive Ethosuximide	
Reporting group title	Placebo
Reporting group description:	
Patients randomised to receive placebo	

Reporting group values	Ethosuximide	Placebo	Total
Number of subjects	7	8	15
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	58.4	52	
standard deviation	± 10.5	± 12.2	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	4	4	8
Ethnicity Units: Subjects			
Caucasian	5	5	10
Non-caucasian	2	3	5
Oncological Diagnosis Units: Subjects			
Breast	1	3	4
Lower GI	2	3	5
Upper GI	1	0	1
Sarcoma	1	0	1
Gynaecological	1	1	2
Myeloma	1	0	1
Urinary Tract	0	1	1
Likely CIPN Causal Agent Units: Subjects			
Paclitaxel	2	5	7

Oxaliplatin	3	3	6
Bortezumab	1	0	1
Docetaxel	1	0	1

End points

End points reporting groups

Reporting group title	Ethosuximide
Reporting group description:	
Patients randomised to receive Ethosuximide	
Reporting group title	Placebo
Reporting group description:	
Patients randomised to receive placebo	

Primary: Reduction of pain intensity from baseline to end-point

End point title	Reduction of pain intensity from baseline to end-point[1]
End point description:	

End point type	Primary
End point timeframe:	
Measured at 6 weeks post randomisation.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed because the trial was terminated early with only 15 of the required 44 patients recruited. In the experimental group, all participants were withdrawn before reaching the 6 week time-point so there was no data to analyse.

End point values	Ethosuximide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Pain score, difference from baseline				
number (not applicable)				

Notes:

[2] - None of the participants randomised to the ethosuximide arm reached the week 6 evaluation point.

[3] - The pain scores were recorded only individually- no analysis was done.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected from the point of randomisation until 3 months after last IMP dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Ethosuximide arm
Reporting group description: Participants that received treatment with Ethosuximide	
Reporting group title	Placebo arm
Reporting group description: Participants randomised to receive placebo	

Serious adverse events	Ethosuximide arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
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: 5 %

Non-serious adverse events	Ethosuximide arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	8 / 8 (100.00%)	

General disorders and administration site conditions			
Pain			
subjects affected / exposed	4 / 7 (57.14%)	5 / 8 (62.50%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 8 (37.50%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 7 (28.57%)	2 / 8 (25.00%)	
occurrences (all)	2	2	
Insomnia			
subjects affected / exposed	4 / 7 (57.14%)	2 / 8 (25.00%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial was terminated early, with only 15 of the 44 required patients recruited.

Notes: