Clinical trial results:
Efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women: The GaPP2 RCT

Summary

EudraCT number	2014-005035-13
Trial protocol	GB
Global end of trial date	13 November 2019

Results information

Result version number	v1 (current)
This version publication date	31 March 2021
First version publication date	31 March 2021

Trial information

Trial identification

Sponsor protocol code	GaPP2

Additional study identifiers

ISRCTN number	ISRCTN77451762
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh
Sponsor organisation address	Little France Crescent, Edinburgh, United Kingdom, EH16 4SA
Public contact	Ann Doust, University of Edinburgh, 0044 1312429492, ann.doust@ed.ac.uk
Scientific contact	Ann Doust, University of Edinburgh, 0044 1312429492, ann.doust@ed.ac.uk
Sponsor organisation name	NHS Lothian
Sponsor organisation address	Little France Crescent, Edinburgh, United Kingdom, EH16 4SA
Public contact	Ann Doust, NHS Lothian, 0044 1312429492, ann.doust@ed.ac.uk
Scientific contact	Ann Doust, NHS Lothian, 0044 1312429492, ann.doust@ed.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	13 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2019
Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test if women with chronic pelvic pain (where no cause for their pain has been found) can be safely treated with gabapentin to gain good pain relief.

Protection of trial subjects:

A Data Monitoring Committee was appointed and met six times throughout the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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: 306
Worldwide total number of subjects	306
EEA total number of subjects	306

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)	306
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited 306 women over a period from November 2015 to March 2019.
Participants were recruited from 39 UK hospital centres.

Pre-assignment

Screening details:

Participants were referred to the research team by their clinical team. Participants entered a screening phase where they were required to return their worst and average pain scores on a numerical scale weekly for four weeks. At least two of the worst NRS pain scores needed to be ≥4 in order for their pain to be considered sufficient for trial.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

300mg starting dose titrated up to 2700mg daily over four weeks (placebo dose equivalent). Maximum tolerated dose maintained for 12 weeks.

Arm title	Active

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Gabapentin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300mg starting dose titrated up to 2700mg daily over four weeks. Maximum tolerated dose maintained for 12 weeks.

Number of subjects in period 1	Placebo	Active
Started	153	153
Completed	153	153

Period 2	
Period 2 title	End of study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 300mg starting dose titrated up to 2700mg daily over four weeks (placebo dose equivalent). Maximum tolerated dose maintained for 12 weeks.	
Arm title	Active
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Gabapentin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 300mg starting dose titrated up to 2700mg daily over four weeks. Maximum tolerated dose maintained for 12 weeks.	

Number of subjects in period 2	Placebo	Active
Started	153	153
Completed	153	153

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Active
Reporting group description: -	

Reporting group values	Placebo	Active	Total
Number of subjects	153	153	306
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)	153	153	306
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30.1	30.5	
standard deviation	± 8.6	± 7.7	-
Gender categorical Units: Subjects			
Female	153	153	306
Male	0	0	0
Education Units: Subjects			
Primary	5	4	9
Secondary	46	47	93
Tertiary	101	101	202
Missing	1	1	2
Dysmenorrhoea Units: Subjects			
Yes	100	100	200
No	53	53	106
Menstruating Units: Subjects			
Yes	108	109	217
No	45	44	89
Current use of sex hormones Units: Subjects			
Yes	99	99	198
No	54	54	108

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Active
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Active
Reporting group description: -	

Primary: End of study Worst NRS pain score

End point title	End of study Worst NRS pain score
End point description:	
End point type	Primary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	124		
Units: Score				
arithmetic mean (standard deviation)				
Worst NRS pain score	7.4 (± 2.2)	7.1 (± 2.6)		

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: End of study Worst NRS pain score	
Comparison groups	Active v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.81
upper limit	0.42

Primary: End of study Average NRS pain score

End point title	End of study Average NRS pain score
End point description:	
End point type	Primary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	123		
Units: Score				
arithmetic mean (standard deviation)				
Average NRS pain score	4.5 (± 2.2)	4.3 (± 2.3)		

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: End of study Average NRS pain score	
Comparison groups	Placebo v Active
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.71
upper limit	0.35

Secondary: End of study SF-12 mental component score

End point title	End of study SF-12 mental component score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	111		
Units: Score				
arithmetic mean (standard deviation)				
End of study SF-12 mental component	42.5 (± 11.1)	41.3 (± 10.6)		

Statistical analyses

Statistical analysis title	End of study -SF36 Mental Component Score
Comparison groups	Placebo v Active
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.11
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-4.6
upper limit	2.39

Secondary: End of study SF-12 physical component score

End point title	End of study SF-12 physical component score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	111		
Units: Score				
arithmetic mean (standard deviation)				
End of study SF-12 physical component	44.6 (± 10.1)	43.8 (± 10.6)		

Statistical analyses

Statistical analysis title	End of study -SF36 Physical Component Score
Comparison groups	Placebo v Active
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-2.27
upper limit	3.24

Secondary: End of study BPI pain interference score

End point title	End of study BPI pain interference score
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: Score				
arithmetic mean (standard deviation)				
End of study BPI pain interference	3.6 (± 2.8)	3.6 (± 2.8)		

Statistical analyses

Statistical analysis title	End of study-BPI Pain Interference score
Comparison groups	Placebo v Active

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.84
upper limit	0.77

Secondary: End of study BFI global fatigue score

End point title	End of study BFI global fatigue score
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: Score				
arithmetic mean (standard deviation)				
End of study BFI global fatigue	4.0 (± 2.7)	4.2 (± 2.5)		

Statistical analyses

Statistical analysis title	End of study-BFI Global Fatigue score
Comparison groups	Placebo v Active
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.65
upper limit	0.89

Secondary: End of study GHQ score

End point title	End of study GHQ score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)	3.0 (± 3.5)	3.8 (± 3.9)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v Active
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.72
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.49
upper limit	1.94

Secondary: End of study WPAIQ activity impairment score

End point title	End of study WPAIQ activity impairment score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	110		
Units: Score				
arithmetic mean (standard deviation)				
End of study WPAIQ activity impairment	38.6 (± 29.6)	39.3 (± 29.0)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v Active
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.77
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-9.66
upper limit	8.12

Secondary: End of study PCQ sore	
End point title	End of study PCQ sore
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	111		
Units: Score				
arithmetic mean (standard deviation)	19.7 (± 12.5)	20.8 (± 14.6)		

Statistical analyses

Statistical analysis title	End of Study PCQ Score
Comparison groups	Placebo v Active

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.48
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-3.24
upper limit	4.2

Secondary: End of study SAQ pleasure score

End point title	End of study SAQ pleasure score
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	83		
Units: Score				
arithmetic mean (standard deviation)	10.9 (± 4.1)	10.8 (± 4.5)		

Statistical analyses

Statistical analysis title	End of study -SAQ Pleasure Score
Comparison groups	Active v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1.84
upper limit	1.56

Secondary: End of study SAQ discomfort score

End point title	End of study SAQ discomfort score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	84		
Units: Score				
arithmetic mean (standard deviation)	3.3 (± 2.0)	3.6 (± 1.9)		

Statistical analyses

Statistical analysis title	End of study-SAQ Discomfort score
Comparison groups	Placebo v Active
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.55
upper limit	0.9

Secondary: End of study SAQ habit score

End point title	End of study SAQ habit score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	83		
Units: Score				
arithmetic mean (standard deviation)	0.9 (± 0.7)	1.1 (± 0.8)		

Statistical analyses

Statistical analysis title	End of study -SAQ habit Score
Comparison groups	Active v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.15
upper limit	0.53

Secondary: End of study PainDETECT score

End point title	End of study PainDETECT score
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	111		
Units: Score				
arithmetic mean (standard deviation)	10.9 (± 6.7)	12.4 (± 6.8)		

Statistical analyses

Statistical analysis title	End of study -PainDETECT Score
Comparison groups	Placebo v Active

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.19
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.74
upper limit	3.12

Secondary: 30% reduction in worst NRS scores	
End point title	30% reduction in worst NRS scores
End point description: 30% reduction in worst NRS scores from baseline.	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	124		
Units: number				
>=30% reduction	21	30		
<30% reduction	101	94		

Statistical analyses

Statistical analysis title	30% Reduction in worst NRS scores
Comparison groups	Placebo v Active
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.38
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.72
upper limit	2.64

Secondary: 30% reduction in average NRS scores	
End point title	30% reduction in average NRS scores
End point description: 30% reduction in average NRS scores from baseline	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	123		
Units: number				
>=30%	37	44		
<30%	84	79		

Statistical analyses

Statistical analysis title	30% Reduction in average NRS scores
Comparison groups	Placebo v Active
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.12
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.7
upper limit	1.8

Secondary: 50% reduction in worst NRS scores	
End point title	50% reduction in worst NRS scores
End point description: 50% reduction in worst NRS scores from baseline	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed				

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.36
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.68
upper limit	2.72

Secondary: End of study WPAIQ Absenteeism score

End point title	End of study WPAIQ Absenteeism score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	83		
Units: score				
arithmetic mean (standard deviation)	4.9 (± 15.1)	10.8 (± 23.5)		

Statistical analyses

Statistical analysis title	End of study-WPAIQ Absenteeism Score
Comparison groups	Placebo v Active
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	5.32
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-2.06
upper limit	12.71

Secondary: End of study WPAIQ Presenteeism score

End point title	End of study WPAIQ Presenteeism score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	72		
Units: score				
arithmetic mean (standard deviation)	38.0 (± 29.6)	36.4 (± 28.4)		

Statistical analyses

Statistical analysis title	End of study-WPAIQ Presenteeism Score
Comparison groups	Active v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.89
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-14.43
upper limit	10.65

Secondary: End of study WPAIQ Productivity Loss score

End point title	End of study WPAIQ Productivity Loss score
End point description:	

End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	72		
Units: score				
arithmetic mean (standard deviation)	39.2 (± 30.7)	39.9 (± 31.1)		

Statistical analyses

Statistical analysis title	End of study-WPAIQ Productivity Loss Score
Comparison groups	Placebo v Active
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-13.73
upper limit	12.87

Secondary: End of study-Number of healthcare visits for pelvic pain: GP

End point title	End of study-Number of healthcare visits for pelvic pain: GP
End point description:	
End point type	Secondary
End point timeframe: End of study	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	111		
Units: number				
None	62	62		
1 appt	21	16		
2 appts	11	16		
3+ appts	15	17		

Statistical analyses

No statistical analyses for this end point

Secondary: End of study-Number of healthcare visits for pelvic pain: Hospital outpatients

End point title	End of study-Number of healthcare visits for pelvic pain: Hospital outpatients

End point description:

End point type	Secondary

End point timeframe:
End of study

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	111		
Units: number				
None	83	89		
1 appt	20	16		
2 appts	4	2		
3+ appts	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: End of study-Number of healthcare visits for pelvic pain: Practice nurse

End point title	End of study-Number of healthcare visits for pelvic pain: Practice nurse

End point description:

End point type	Secondary

End point timeframe:
End of study

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: number				
None	103	99		
1 appt	3	8		
2 appts	1	1		
3+ appts	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: End of study-Number of healthcare visits for pelvic pain: Physiotherapist

End point title	End of study-Number of healthcare visits for pelvic pain: Physiotherapist

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: number				
None	105	107		
1 appt	0	1		
2 appts	1	1		
3+ appts	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: End of study-Number of healthcare visits for pelvic pain: Other

End point title	End of study-Number of healthcare visits for pelvic pain: Other

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: number				
None	97	99		
1 appt	5	6		
2 appts	3	2		
3+ appts	4	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From time of randomisation to end of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	4
Reporting groups	
Reporting group title	Active arm
Reporting group description: -	
Reporting group title	Placebo arm
Reporting group description: -	

Serious adverse events	Active arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 153 (6.54%)	3 / 153 (1.96%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Hypotension			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Scleritis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Perforated uterus			

subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst removal			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Cholecystitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Paranoia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest infection			

subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (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: 0.05 %

Non-serious adverse events	Active arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 153 (81.05%)	116 / 153 (75.82%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Sterilisation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Mole excision			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Tonsillectomy			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Lumbar puncture normal			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	2	0	
Cyst removal			

subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Cystoscopy			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 153 (4.58%)	1 / 153 (0.65%)	
occurrences (all)	8	1	
Thirst			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
mental fogginess			
subjects affected / exposed	4 / 153 (2.61%)	0 / 153 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Allergic respiratory symptom			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Breast abscess			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Breast pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	0 / 153 (0.00%)	2 / 153 (1.31%)	
occurrences (all)	0	2	
Menorrhagia			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Intermenstrual bleeding			

subjects affected / exposed	0 / 153 (0.00%)	6 / 153 (3.92%)	
occurrences (all)	0	6	
Vaginal discharge			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	2	0	
Pelvic pain			
subjects affected / exposed	6 / 153 (3.92%)	3 / 153 (1.96%)	
occurrences (all)	6	4	
Raised CA-125			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 153 (1.96%)	2 / 153 (1.31%)	
occurrences (all)	3	2	
Asthma			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Wheezing			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 153 (1.31%)	1 / 153 (0.65%)	
occurrences (all)	2	1	
Anxiety			
subjects affected / exposed	2 / 153 (1.31%)	1 / 153 (0.65%)	
occurrences (all)	3	1	
Hallucination			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	2	0	
Obsessive-compulsive symptom			

Headache			
subjects affected / exposed	4 / 153 (2.61%)	7 / 153 (4.58%)	
occurrences (all)	5	10	
Loss of consciousness			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	4 / 153 (2.61%)	4 / 153 (2.61%)	
occurrences (all)	4	5	
Paresthesia			
subjects affected / exposed	3 / 153 (1.96%)	1 / 153 (0.65%)	
occurrences (all)	3	1	
Sciatica			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Eye disorders			
Twitch			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Visual disturbances			
subjects affected / exposed	3 / 153 (1.96%)	2 / 153 (1.31%)	
occurrences (all)	3	2	
Blistering of eye			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Epigastric discomfort			
subjects affected / exposed	0 / 153 (0.00%)	2 / 153 (1.31%)	
occurrences (all)	0	2	
Abdominal distension			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	0 / 153 (0.00%)	2 / 153 (1.31%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	2 / 153 (1.31%)	4 / 153 (2.61%)	
occurrences (all)	3	4	
Dry mouth			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	3	0	
Haemorrhoids			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	2 / 153 (1.31%)	
occurrences (all)	1	2	
Abdominal discomfort			
subjects affected / exposed	6 / 153 (3.92%)	7 / 153 (4.58%)	
occurrences (all)	9	8	
Tooth abscess			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 153 (1.31%)	6 / 153 (3.92%)	
occurrences (all)	3	6	
Nausea			
subjects affected / exposed	0 / 153 (0.00%)	6 / 153 (3.92%)	
occurrences (all)	0	6	
Geographic tongue			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	

Facial spots			
subjects affected / exposed	1 / 153 (0.65%)	2 / 153 (1.31%)	
occurrences (all)	1	2	
Itch			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	2 / 153 (1.31%)	3 / 153 (1.96%)	
occurrences (all)	2	3	
Haematinuria			
subjects affected / exposed	0 / 153 (0.00%)	2 / 153 (1.31%)	
occurrences (all)	0	2	
Renal colic			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 153 (1.96%)	0 / 153 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	2 / 153 (1.31%)	4 / 153 (2.61%)	
occurrences (all)	3	5	
Intervertebral disc displacement			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc pseudobulging			

subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Ankle impingement			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Loin pain			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Fracture			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	5 / 153 (3.27%)	5 / 153 (3.27%)	
occurrences (all)	5	5	
Chlamydial infection			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 153 (0.65%)	4 / 153 (2.61%)	
occurrences (all)	1	4	
Ear infection			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	5 / 153 (3.27%)	1 / 153 (0.65%)	
occurrences (all)	5	1	
Gingivitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	

Helicobacter infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 153 (0.65%)	3 / 153 (1.96%)	
occurrences (all)	1	3	
Candida infection			
subjects affected / exposed	0 / 153 (0.00%)	2 / 153 (1.31%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	7 / 153 (4.58%)	2 / 153 (1.31%)	
occurrences (all)	10	2	
Viral infection			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	2	0	
Folate deficiency			
subjects affected / exposed	2 / 153 (1.31%)	0 / 153 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			

subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 153 (0.65%)	1 / 153 (0.65%)	
occurrences (all)	1	1	
Anaemia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2015	1. We have included more details with regard to a number of the objectives and the criteria for entry to the trial. These are indicated in track changes within the protocol. 2. We have also added an additional embedded pharmacogenetic substudy to investigate the influence of genetic variation on gabapentin efficacy and potential intolerance, and the potential for stratification of patients with likely drug response based on genetic profiles.
22 February 2016	Insertion of ISCTRN and funding references Clarification of unblinding procedures Update of contact details Removal of analgesic use while in study details to reflect the analgesic use may reduce. This was written in error in the original protocol as we hope that analgesic use will decrease over the course of the study for some of the participants. Removal of heat stimulus from fMRI process. The thermal equipment was temperamental in the mock scans we ran and looking at the pilot data the pin pricks gave us the desired effect on the brain so it was felt that the thermal stimulus was unnecessary and prolonged the scanning process. Change of fMRI PIS to remove thermal stimuli Addition of pt emergency card - to identify participants in case of emergencies.
14 March 2016	Changes to the SmPC for gabapentin 300 mgs
03 May 2016	Amendment to emergency card
28 February 2017	Addition of a healthy volunteer are to the fMRI substudy. On monitoring the first patients at each site, certain deviations were noted. These were in the timing of visit 5. The last text pain score is collected at the end of week 16 and therefore unblinding cannot take place during this week so for clarity this has been changed to week 17. Participants increase and decrease their doses of gabapentin throughout the course of the trial which reflects real life situations and therefore these fluctuations will be captured but will not be seen as a deviation. The use of rescue analgesia will be restricted only by the SmPC and not by the protocol as these did not reflect common clinical practices. SmPC for gabapentin 300mgs has been updated. RSI information has changed. All sites notified of the change. The annual reporting period is coming to an end and therefore the SmPC can now be changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

15 December 2017	In December 2017, we had to stop randomising participants to treatment while we waited for the outcome of our costed extension request. In February 2018, we were informed that our costed extension had been granted. We instructed Sharp Services to produce our third campaign of IMP shortly after this date, but the factory had to close in March due to issues with their production unit.	16 April 2018

Notes:

Limitations and caveats

None reported