Clinical trial results:
The effect of bupropion in peripheral neuropathic pain. A randomized, double-blind, placebo-controlled study.

Summary

EudraCT number	2019-000243-27
Trial protocol	DK
Global end of trial date	13 October 2022

Results information

Result version number	v1 (current)
This version publication date	24 January 2025
First version publication date	24 January 2025

Trial information

Trial identification

Sponsor protocol code	BUPROPION2019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	J.B. Winløwsvej 4, Odense , Denmark, 5000
Public contact	Neuromuscular Clinic, Odense University Hospital, 0045 65412471, soeren.sindrup@rsyd.dk
Scientific contact	Neuromuscular Clinic, Odense University Hospital, 0045 65412471, soeren.sindrup@rsyd.dk

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	04 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2022
Global end of trial reached?	Yes
Global end of trial date	13 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to determine if bupropion relieves peripheral neuropathic pain

Protection of trial subjects:

None.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from two counties (Region of Southern Denmark and Region Midt) in Denmark from 3 Sept. 2020 to 13 Oct. 2022. Patients were recruited from the outpatient clinic at the Department of Neurology at Odense University Hospital and Aarhus University, as well as from advertisement on Facebook.

Pre-assignment

Screening details:

Most important inclusion criteria:
Age ≥ 18 years, probable/definite peripheral neuropathic pain for at least 3 months, weekly average of daily pain intensity > 4 (0-10 NRS).
Most important exclusion criteria:
Other cause of pain, major depression within 6 months, treatment with antidepressants, opioids and drugs with potential interaction.

Pre-assignment period milestones

Number of subjects started	140
Number of subjects completed	123

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Comorbidity: 1
Reason: Number of subjects	Concomitant medication that could not be withdrawn: 1
Reason: Number of subjects	Enrolled in another study: 1
Reason: Number of subjects	Low pain score (NRS < 4): 4
Reason: Number of subjects	Other cause of pain in same area: 2
Reason: Number of subjects	Not neuropathic pain: 3

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline to bupropion

Arm description:

Baseline period with no treatment before bupropion

Arm type	Baseline no treatment
Investigational medicinal product name	No investigational medicinal product assigned in this arm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

N/A

Arm title	Baseline to placebo

Arm description:

Baseline period with no treatment before placebo

Arm type	Baseline no treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Baseline to bupropion	Baseline to placebo
Started	64	59
Completed	64	59

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: Patients were excluded before baseline and allocation was started due to the reasons listed in the 'pre-assignment period'-section

Period 2

Period 2 title	Treatment periods summary
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo capsules identical to terbutaline and imipramine capsules. Double-dummy technique. Randomization was done by Sygehus Apotek Fyn using a computer-generated randomization list using block size unknown to the investigators

Arms

Are arms mutually exclusive?	Yes
Arm title	Bupropion

Arm description:

Treatment with bupropion 150 mg to 300 mg daily.

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

Dosage and administration details:

150 mg once a day for 1 week, followed by 150 mg twice a day for 5 weeks.
Age >= 75 years 150 mg a day for 6 weeks.

Arm title	Placebo

Arm description:

Treatment with placebo capsules

Arm type	Placebo

Investigational medicinal product name	Placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage (number ogf capsules) corresponding to number of capsules with active substances

Number of subjects in period 2	Bupropion	Placebo
Started	64	59
Completed	55	56
Not completed	9	3
Adverse event, non-fatal	7	-
Too painful	2	1
Lost to follow-up	-	2

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	123	123	
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	57		
full range (min-max)	18 to 81	-	
Gender categorical Units: Subjects			
Female	62	62	
Male	61	61	

End points

End points reporting groups

Reporting group title	Baseline to bupropion
Reporting group description: Baseline period with no treatment before bupropion	
Reporting group title	Baseline to placebo
Reporting group description: Baseline period with no treatment before placebo	
Reporting group title	Bupropion
Reporting group description: Treatment with bupropion 150 mg to 300 mg daily.	
Reporting group title	Placebo
Reporting group description: Treatment with placebo capsules	
Subject analysis set title	Intention to treat analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified intention to treat analysis set, subjects with data from 1 or 2 treatment periods	

Primary: Numeric Rating of average daily pain (NRS), weekly median

End point title	Numeric Rating of average daily pain (NRS), weekly median
End point description: Average daily pain NRS score 0-10, 0 = no pain and 10 = worst possible pain.	
End point type	Primary
End point timeframe: Weekly median of the average daily pain from the each of the 6 weeks in each treatment period and the 2 baseline periods were included in the analysis.	

End point values	Baseline to bupropion	Baseline to placebo	Bupropion	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	59[1]	59	59[2]	59
Units: NRS 0-10 points				
arithmetic mean (standard deviation)	6.36 (± 0.16)	6.17 (± 0.18)	5.52 (± 0.23)	5.79 (± 0.23)

Notes:

[1] - 4 subjects excluded due to missing data (no diary handed in), 1 subject too short datacollection

[2] - 4 subjects excluded due to missing data (no diary handed in), 1 subject too short datacollection

End point values	Intention to treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	118			
Units: NRS 0-10 points				
arithmetic mean (standard deviation)	5.52 (± 0.23)			

Statistical analyses

Statistical analysis title	Primary outcome in general linear model

Statistical analysis description:

General linear model Including bupropion treatment weeks 1-6 and corresponding baseline period compared to placebo treatment weeks 1-6 and corresponding baseline period in a cross-over design.

Comparison groups	Baseline to bupropion v Baseline to placebo v Bupropion v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After three weeks in each treatment period with bupropion and placebo. At the end of each treatment period. At the follow-up phone call at the end of study. Patients could contact the investigator via phone at any timepoint during the study period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Bupropion
Reporting group description:	
End of treatment with bupropion	
Reporting group title	Placebo
Reporting group description:	
End of treatment with placebo	

Serious adverse events	Bupropion	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 62 (3.23%)	1 / 59 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Necrosis ischaemic	Additional description: Necrosis of toe related to diabetes mellitus. Planned amputation.		
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (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: 5 %

Non-serious adverse events	Bupropion	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 62 (54.84%)	20 / 59 (33.90%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 62 (8.06%)	11 / 59 (18.64%)	
occurrences (all)	5	11	
paresthesia			
subjects affected / exposed	5 / 62 (8.06%)	1 / 59 (1.69%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 62 (11.29%)	0 / 59 (0.00%)	
occurrences (all)	7	0	
Dry mouth			
subjects affected / exposed	5 / 62 (8.06%)	0 / 59 (0.00%)	
occurrences (all)	5	0	
Abdominal pain			
subjects affected / exposed	5 / 62 (8.06%)	3 / 59 (5.08%)	
occurrences (all)	5	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 62 (17.74%)	5 / 59 (8.47%)	
occurrences (all)	11	5	
Fatigue			
subjects affected / exposed	5 / 62 (8.06%)	1 / 59 (1.69%)	
occurrences (all)	5	1	

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

None reported