Clinical trial results:
Tetra-hydro-cannabinol, cannabidiol and their combination for the treatment of peripheral neuropathic pain. A randomised placebo-controlled trial.

Summary

EudraCT number	2017-005198-38
Trial protocol	DK
Global end of trial date	03 May 2021

Results information

Result version number	v1 (current)
This version publication date	12 October 2022
First version publication date	12 October 2022

Trial information

Trial identification

Sponsor protocol code	CANNA1

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. Winsløws Vej 4, Odense, Denmark,
Public contact	Neuromuscular team, Odense University Hospital, 0045 65412471, soeren.sindrup@rsyd.dk
Scientific contact	Neuromuscular team, 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	01 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2021
Global end of trial reached?	Yes
Global end of trial date	03 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to test if the primary active components of cannabis (tetra-hydro-cannabinol and cannabidiol) provide a clinically relevant pain relief in peripheral neuropathic pain.

Protection of trial subjects:

Escape medication could be used and patients could continue some usual neuropathic pain treatments (gabapentin/pregabalin/antidepressants)

Background therapy:

Placebo

Evidence for comparator:

None

Actual start date of recruitment	02 April 2018
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: 145
Worldwide total number of subjects	145
EEA total number of subjects	145

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)	74
From 65 to 84 years	70
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The patients were recruited in Denmark during the period December 2018 to May 2021.

Pre-assignment

Screening details:

The patients were recruited from out-patient clinics, adds in local media, and through social media. 169 patients were sreened for participation and 145 patients entered the study. 115 patients were randomised for treatment and the main reason to not being randomised were low pain score, withdrawn consent, and co-morbidities.

Pre-assignment period milestones

Number of subjects started	145
Number of subjects completed	115

Pre-assignment subject non-completion reasons

Reason: Number of subjects	driving ban: 1
Reason: Number of subjects	alcohol consumption: 2
Reason: Number of subjects	co-morbidities: 5
Reason: Number of subjects	Consent withdrawn by subject: 8
Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	low pain score: 2
Reason: Number of subjects	unknown: 7
Reason: Number of subjects	Physician decision: 3

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Allocation to treatment via computer generated list.
Study medication of identical appearance and smell.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cannabidiol

Arm description:

Treatment with cannabidiol flexible dose from 5 mg to 50 mg

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

Dosage and administration details:

Dosing twice daily.
Starting dose 5 mg/day and maximum dose 50 mg/day.

Arm title	Tetra-hydro-cannabinol

Arm description:

Treatment with flexible dose of tetra-hydro-cannabinol from 2.5 mg/day to 25 mg/day.

Arm type	Experimental
Investigational medicinal product name	Tetra-hydro-cannabinol
Investigational medicinal product code	
Other name	THC
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosed twice daily and dosage from 2.5 mg/day to 25 mg/day

Arm title	Combination

Arm description:

Flexible dosing of combination of cannabidiol and tetra-hydro-cannabinol dosage 5 mg/2.5 mg to 50 mg/25 mg daily

Arm type	Experimental
Investigational medicinal product name	Cannabidiol plus tetra-hydro-cannabinol
Investigational medicinal product code	
Other name	CBD/THC
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosed twice daily. Dosage from CBD 5 mg/day and THC 2.5 mg/day to CBD 50 mg/day and THC 25 mg/day

Arm title	Placebo

Arm description:

Placebo treatment

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

Dosage and administration details:

Dosedtwiced daily. Dose from 1 capsule daily to 10 capsules daily.

Number of subjects in period 1[1]	Cannabidiol	Tetra-hydro-cannabinol	Combination
Started	27	28	30
Completed	23	24	24
Not completed	4	4	6
unknown	1	-	1

co-morbidities	-	-	-
Adverse event, non-fatal	2	1	4
co-morbidity	-	2	-
hospitalization	-	1	1
Lack of efficacy	1	-	-

Number of subjects in period 1[1]	Placebo
Started	30
Completed	25
Not completed	5
unknown	1
co-morbidities	3
Adverse event, non-fatal	-
co-morbidity	-
hospitalization	-
Lack of efficacy	1

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: 145 subjects entered the pre-assignment period and 115 entered the period1 including the baseline and treatment periods.

Baseline characteristics

Reporting groups	
Reporting group title	Cannabidiol
Reporting group description:	
Treatment with cannabidiol flexible dose from 5 mg to 50 mg	
Reporting group title	Tetra-hydro-cannabinol
Reporting group description:	
Treatment with flexible dose of tetra-hydro-cannabinol from 2.5 mg/day to 25 mg/day.	
Reporting group title	Combination
Reporting group description:	
Flexible dosing of combination of cannabidiol and tetra-hydro-cannabinol dosage 5 mg/2.5 mg to 50 mg/25 mg daily	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	

Reporting group values	Cannabidiol	Tetra-hydro-cannabinol	Combination
Number of subjects	27	28	30
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years			
Units: years			
median	64	62	68
full range (min-max)	43 to 79	27 to 83	22 to 95
Gender categorical Units: Subjects			
Female	13	13	21
Male	14	15	9

Reporting group values	Placebo	Total	
Number of subjects	30	115	
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			
Age in years			
Units: years			
median	66		
full range (min-max)	39 to 78	-	
Gender categorical			
Units: Subjects			
Female	17	64	
Male	13	51	

Subject analysis sets

Subject analysis set title	Intention -to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects being randomised and starting treatment.

Reporting group values	Intention -to-treat		
Number of subjects	115		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age in years			
Units: years			
median	65		
full range (min-max)	22 to 95		
Gender categorical			
Units: Subjects			
Female	64		
Male	51		

End points

End points reporting groups

Reporting group title	Cannabidiol
Reporting group description:	
Treatment with cannabidiol flexible dose from 5 mg to 50 mg	
Reporting group title	Tetra-hydro-cannabinol
Reporting group description:	
Treatment with flexible dose of tetra-hydro-cannabinol from 2.5 mg/day to 25 mg/day.	
Reporting group title	Combination
Reporting group description:	
Flexible dosing of combination of cannabidiol and tetra-hydro-cannabinol dosage 5 mg/2.5 mg to 50 mg/25 mg daily	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	
Subject analysis set title	Intention -to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects being randomised and starting treatment.	

Primary: Change in average weekly pain NRS score

End point title	Change in average weekly pain NRS score
End point description:	
Averega daily pain was scored daily and recorded and an average weekly scores was calculated. From these average weekly pain scores changes from the baseline week to each of the treatment weeks were calculated. In results table only change from baseline to week 8 given.	
End point type	Primary
End point timeframe:	
The change in pain score (average weekly score) from baseline to each of the treatment weeks 1 to 8 were used.	

End point values	Cannabidiol	Tetra-hydro-cannabinol	Combination	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	30	30
Units: NRS points 0-10				
arithmetic mean (standard deviation)	-0.58 (± 1.74)	-1.43 (± 2.09)	-1.93 (± 1.90)	-1.86 (± 2.22)

End point values	Intention -to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	115			
Units: NRS points 0-10				
arithmetic mean (standard deviation)	-1.47 (± 2.04)			

Statistical analyses

Statistical analysis title	General linear model on change in pain scores

Statistical analysis description:

General linear model with changes in pain scores from baseline to each treatment week (1 trough 8) for each treatment (CBD; THC CBD/THC) compared to placebo.

Comparison groups	Cannabidiol v Tetra-hydro-cannabinol v Combination v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.02 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[1] - Analysis model taking all treatment weeks into account.

[2] - 0.05 significance level corrected for multiple comparisons to 0.02 (0.05/3).
In GLM with all treatment weeks:
Placebo vs Cannabidiol: 0.04
Placebo vs Tetra-hydro-cannabinol: 0.41
Placebo vs Combination Cannabidiol and tetra-hydro-cannabinol: 0.60

Secondary: 30% pain relief

End point title	30% pain relief

End point description:

Number of patients that at the end of week 8 had had a reduction in pain score from baseline of 30% or more.

End point type	Secondary

End point timeframe:

Baseline to week 8 of treatment.

End point values	Cannabidiol	Tetra-hydro-cannabinol	Combination	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	30	30
Units: subjects				
Response	9	12	18	17
Non-response	18	16	12	13

End point values	Intention -to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	115			
Units: subjects				
Response	56			
Non-response	59			

Statistical analyses

Statistical analysis title	Comparison of proportions

Statistical analysis description:

Comparison of each of the treatment arms with the placebo arm

Comparison groups	Cannabidiol v Tetra-hydro-cannabinol v Combination v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02 [3]
Method	Fisher exact

Notes:

[3] - Usual significance level 0.05 corrected for multiple comparisons to 0.02 (0.05/3)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events reported as "present" during baseline and treatment period	
Assessment type	Systematic

Dictionary used	
Dictionary name	None
Dictionary version	0

Reporting groups	
Reporting group title	Baseline
Reporting group description: -	
Reporting group title	Cannabidiol
Reporting group description: -	
Reporting group title	Tetra-hydro-cannabidiol
Reporting group description: -	
Reporting group title	Combination
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Baseline	Cannabidiol	Tetra-hydro-cannabidiol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 114 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Combination	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Baseline	Cannabidiol	Tetra-hydro-cannabidiol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 114 (99.12%)	16 / 24 (66.67%)	22 / 26 (84.62%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 114 (2.63%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Dry mouth			
subjects affected / exposed	28 / 114 (24.56%)	7 / 24 (29.17%)	8 / 26 (30.77%)
occurrences (all)	28	7	8
Headache			
subjects affected / exposed	13 / 114 (11.40%)	2 / 24 (8.33%)	3 / 26 (11.54%)
occurrences (all)	13	2	3
Nightmare			
subjects affected / exposed	3 / 114 (2.63%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Dizziness			
subjects affected / exposed	12 / 114 (10.53%)	1 / 24 (4.17%)	3 / 26 (11.54%)
occurrences (all)	12	1	3
Drowsiness			
subjects affected / exposed	29 / 114 (25.44%)	2 / 24 (8.33%)	6 / 26 (23.08%)
occurrences (all)	29	2	6
Facial flush			
subjects affected / exposed	8 / 114 (7.02%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences (all)	8	1	2
Blurred vision			
subjects affected / exposed	6 / 114 (5.26%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	6	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	10 / 114 (8.77%)	1 / 24 (4.17%)	3 / 26 (11.54%)
occurrences (all)	10	1	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 114 (2.63%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0

Nausea			
subjects affected / exposed	1 / 114 (0.88%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	3 / 114 (2.63%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	3	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 114 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	2 / 114 (1.75%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Muscle pain			
subjects affected / exposed	30 / 114 (26.32%)	8 / 24 (33.33%)	6 / 26 (23.08%)
occurrences (all)	30	8	6

Non-serious adverse events	Combination	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	17 / 25 (68.00%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dry mouth			
subjects affected / exposed	9 / 27 (33.33%)	7 / 25 (28.00%)	
occurrences (all)	9	7	
Headache			
subjects affected / exposed	4 / 27 (14.81%)	0 / 25 (0.00%)	
occurrences (all)	4	0	
Nightmare			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Dizziness			

subjects affected / exposed	2 / 27 (7.41%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Drowsiness			
subjects affected / exposed	8 / 27 (29.63%)	5 / 25 (20.00%)	
occurrences (all)	8	5	
Facial flush			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Blurred vision			
subjects affected / exposed	1 / 27 (3.70%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 27 (11.11%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Nervousness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Muscle pain			
subjects affected / exposed	1 / 27 (3.70%)	3 / 25 (12.00%)	
occurrences (all)	1	3	

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