Clinical trial results:
A Mechanism Based Proof of Concept Study of the Effects of Duloxetine in the Treatment of Patients with Osteoarthritic Knee Pain

Summary

EudraCT number	2019-003437-42
Trial protocol	DK
Global end of trial date	01 July 2021

Results information

Result version number	v1 (current)
This version publication date	18 August 2022
First version publication date	18 August 2022
Summary attachment (see zip file)	Published manuscript (European Journal of Pain - 2022 - Petersen - The effect of duloxetine on mechanistic pain profiles cognit.pdf)

Trial information

Trial identification

Sponsor protocol code	DULKOA2019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04224584
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aalborg University
Sponsor organisation address	Fredrik Bajers Vej 7, Aalborg, Denmark, 9220
Public contact	Professor, Lars Arendt-Nielsen, +45 9940 8827, LAN@hst.aau.dk
Scientific contact	Professor, Lars Arendt-Nielsen, +45 9940 8827, LAN@hst.aau.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	17 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2021
Global end of trial reached?	Yes
Global end of trial date	01 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess which experimental pain mechanisms are modulated by Duloxetine compared to placebo in patients with knee osteoarthritis.

Protection of trial subjects:

The trial was continuously monitored by the Good Clinical Practice (GCP) Unit of Aalborg University Hospital, externally audited by the Danish Medicines Agency, and was conducted in accordance with The Helsinki Declaration, GCP, and all applicable Danish regulatory requirements. Informed consent was obtained from all participants.
All adverse events were monitored continuously .

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2019
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	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	0
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited through Synexus/C4Pain, Aalborg, Denmark (a contracting research organization).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 4

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Duloxetine

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Duloxetin Lilly
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Treatment periods included a 2-week titration period (week 1 (7 days): 20 mg/daily, week 2 (7 days): 40 mg/daily), a 14-week full treatment period (week 3-16 (70 days): 60 mg/daily) followed by a 2-week discontinuation period (week 17 (7 days): 40 mg/daily, week 18 (7 days): 20 mg/daily).

Arm title	Placebo

Arm description: -

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:

Treatment periods included a 2-week titration period (week 1 (7 days): 20 mg/daily, week 2 (7 days): 40 mg/daily), a 14-week full treatment period (week 3-16 (70 days): 60 mg/daily) followed by a 2-week discontinuation period (week 17 (7 days): 40 mg/daily, week 18 (7 days): 20 mg/daily).

Number of subjects in period 1[1]	Duloxetine	Placebo
Started	18	18
Completed	13	14
Not completed	5	4
Consent withdrawn by subject	2	2
Adverse event, non-fatal	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: This is a cross-over trial but the system cannot be setup for this. Please see our published results (Open Access) from there trial here: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ejp.1988

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Duloxetine

Arm description: -

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

Dosage and administration details:

Treatment periods included a 2-week titration period (week 1 (7 days): 20 mg/daily, week 2 (7 days): 40 mg/daily), a 14-week full treatment period (week 3-16 (70 days): 60 mg/daily) followed by a 2-week discontinuation period (week 17 (7 days): 40 mg/daily, week 18 (7 days): 20 mg/daily).

Arm title	Placebo

Arm description: -

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:

Treatment periods included a 2-week titration period (week 1 (7 days): 20 mg/daily, week 2 (7 days): 40 mg/daily), a 14-week full treatment period (week 3-16 (70 days): 60 mg/daily) followed by a 2-week discontinuation period (week 17 (7 days): 40 mg/daily, week 18 (7 days): 20 mg/daily).

Number of subjects in period 2	Duloxetine	Placebo
Started	14	13
Completed	12	13
Not completed	2	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period 1

Reporting group description: -

Reporting group values	Treatment period 1	Total	
Number of subjects	36	36	
Age categorical			
Women and men, 40– 75 years of age, with OA of the knee, who agreed to participate and filled in an informed consent, were included.			
Units: Subjects			
Adults (18-64 years)	13	13	
From 65-84 years	23	23	
Gender categorical Units: Subjects			
Female	23	23	
Male	13	13	

Subject analysis sets

Subject analysis set title	38
Subject analysis set type	Per protocol

Subject analysis set description:

Patients how completed (N=25) the trial are in this analysis.

Reporting group values	38		
Number of subjects	25		
Age categorical			
Women and men, 40– 75 years of age, with OA of the knee, who agreed to participate and filled in an informed consent, were included.			
Units: Subjects			
Adults (18-64 years)	9		
From 65-84 years	16		
Gender categorical Units: Subjects			
Female	18		
Male	7		

End points

End points reporting groups

Reporting group title	Duloxetine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Duloxetine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	38
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients how completed (N=25) the trial are in this analysis.	

Primary: Pressure pain thresholds

End point title	Pressure pain thresholds
End point description:	
End point type	Primary
End point timeframe:	
Effect of treatment (absolut difference between follow-up and baseline) when comparing the two treatments (placebo vs. duloxetine)	

End point values	Duloxetine	Placebo	Duloxetine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	14	12	13
Units: kilopascale				
arithmetic mean (standard deviation)	17.31 (± 6.44)	20.1 (± 7.87)	16.66 (± 6.74)	16.37 (± 7.82)

Attachments (see zip file)	Published manuscript/European Journal of Pain - 2022 -

Statistical analyses

Statistical analysis title	Treatment effect of pressure pain thresholds
Comparison groups	Duloxetine v Placebo
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.303
Method	ANOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed at each visit and by contact to the research team.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	1

Reporting groups

Reporting group title	Duloxetine
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Duloxetine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
evere headache, palpitations, and difficulty breathing	Additional description: One serious adverse event occurred during the duloxetine treatment period where one patient experienced severe headache, palpitations, and difficulty breathing, and the patient was hospitalized for 1 day to ensure safety		
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (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	Duloxetine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	22 / 31 (70.97%)	
Vascular disorders			
Dry mouth			
subjects affected / exposed	13 / 32 (40.63%)	7 / 31 (22.58%)	
occurrences (all)	13	7	
Cardiac disorders			

Fatigue subjects affected / exposed occurrences (all)	9 / 32 (28.13%) 9	4 / 31 (12.90%) 5	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	14 / 32 (43.75%) 14	11 / 31 (35.48%) 11	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35638317