Clinical trial results:
Direct comparison of intra-articular saline injections with an education plus exercise program for treatment of knee osteoarthritis symptoms: A randomised, open label, controlled, evidence based trial

Summary

EudraCT number	2019-000809-71
Trial protocol	DK
Global end of trial date	01 November 2021

Results information

Result version number	v1 (current)
This version publication date	22 December 2021
First version publication date	22 December 2021
Summary attachment (see zip file)	Scientific article (Bandak E, Ann Rheum Dis 2021 (DISCO GLAD vs Saline).pdf)

Trial information

Trial identification

Sponsor protocol code	APPI2-PT-2019-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03843931
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Parker Institute, Frederiksberg Hospital
Sponsor organisation address	Ndr. Fasanvej 57, Copenhagen, Denmark, 2000
Public contact	Primary/ Principal Investigator, The Parker Institute, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark, 45 38164155, henning.bliddal@regionh.dk
Scientific contact	Primary/ Principal Investigator, The Parker Institute, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark, 45 38164155, henning.bliddal@regionh.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 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2020
Global end of trial reached?	Yes
Global end of trial date	01 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare a widely used education plus exercise program (the GLA:D program) with intra-articular saline injections as treatments of knee OA symptoms

Protection of trial subjects:

The trial was open-label and any adverse event reported by the participants were handled by scheduling an appointment with an investigator

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 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: 206
Worldwide total number of subjects	206
EEA total number of subjects	206

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)	67
From 65 to 84 years	133
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Between 30 July 2019 and 17 September 2020, participants were recruited from the OA outpatient's clinic at Bispebjerg-Frederiksberg Hospital, Denmark

Pre-assignment

Screening details:

544 individuals were prescreened by telephone, of which 207 were ineligible and 10 declined clinical screening.
317 had their eligibility assessed by clinical screening, of which 109 were not eligible and 2 were ineligible but were not randomised.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label trial neither health professionals delivering the interventions, nor participants were blinded to treatment allocation. Outcome assessors were blinded to allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Exercise and Education

Arm description:

The GLA:D program

Arm type	behavioural/exercise

No investigational medicinal product assigned in this arm

Arm title	Open Label Placebo

Arm description:

Intra-articular injections of 5 ml saline

Arm type	Placebo
Investigational medicinal product name	Natriumklorid isotonisk "SAD"
Investigational medicinal product code	V07AB
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

1 injection every two weeks over a period of 8 weeks; 4 injections of 5 ml in total

Number of subjects in period 1	Exercise and Education	Open Label Placebo
Started	102	104
Week 9	97	99
Week 12	91	91
Completed	91	91
Not completed	11	13

Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	2
Other reasons	4	6
COVID19 trial suspension	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Exercise and Education
Reporting group description:	
The GLA:D program	
Reporting group title	Open Label Placebo
Reporting group description:	
Intra-articular injections of 5 ml saline	

Reporting group values	Exercise and Education	Open Label Placebo	Total
Number of subjects	102	104	206
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)	27	47	74
From 65-84 years	71	55	126
85 years and over	4	2	6
Age continuous Units: years			
arithmetic mean	70.1	66.7	
standard deviation	± 8.3	± 8.2	-
Gender categorical Units: Subjects			
Female	45	49	94
Male	57	55	112

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

Subject analysis set description:

The primary analysis was performed using the intention-to- treat (ITT) population; patients were assessed and analysed as members of their randomised groups, irrespective of adherence to the treatments.

Reporting group values	ITT		
Number of subjects	206		
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)	74		
From 65-84 years	126		
85 years and over	6		
Age continuous			
Units: years			
arithmetic mean	68.4		
standard deviation	± 8.4		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Exercise and Education
Reporting group description: The GLA:D program	
Reporting group title	Open Label Placebo
Reporting group description: Intra-articular injections of 5 ml saline	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary analysis was performed using the intention-to- treat (ITT) population; patients were assessed and analysed as members of their randomised groups, irrespective of adherence to the treatments.	

Primary: change from baseline in the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale

End point title	change from baseline in the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale
End point description:	
End point type	Primary
End point timeframe: Week 9	

End point values	Exercise and Education	Open Label Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: points				
arithmetic mean (confidence interval 95%)	10.0 (7.0 to 12.9)	7.3 (4.4 to 10.2)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Exercise and Education v Open Label Placebo
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (net)
Point estimate	2.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	6

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to week 12	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Exercise and Education
Reporting group description: The GLA:D program	
Reporting group title	Open Label Placebo
Reporting group description: Intra-articular injections of 5 ml saline	

Serious adverse events	Exercise and Education	Open Label Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 99 (5.05%)	5 / 103 (4.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
coloscopy			
subjects affected / exposed	1 / 99 (1.01%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	2 / 99 (2.02%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			

subjects affected / exposed	0 / 99 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 99 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 99 (1.01%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abscess			
subjects affected / exposed	0 / 99 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip disarticulation			
subjects affected / exposed	0 / 99 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Knee pain		
subjects affected / exposed	1 / 99 (1.01%)	0 / 103 (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	Exercise and Education	Open Label Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 99 (34.34%)	40 / 103 (38.83%)	
Injury, poisoning and procedural complications			

Procedural complication			
subjects affected / exposed	7 / 99 (7.07%)	1 / 103 (0.97%)	
occurrences (all)	7	1	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	5 / 99 (5.05%)	3 / 103 (2.91%)	
occurrences (all)	5	6	
Skin and subcutaneous tissue disorders			
Injection related reaction			
subjects affected / exposed	0 / 99 (0.00%)	3 / 103 (2.91%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Pain exacerbation			
subjects affected / exposed	26 / 99 (26.26%)	37 / 103 (35.92%)	
occurrences (all)	34	38	
Infections and infestations			
Infection			
subjects affected / exposed	3 / 99 (3.03%)	0 / 103 (0.00%)	
occurrences (all)	3	0	

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/34844929