Clinical trial results:
A Double-Blind, Randomised, Exploratory Study to Investigate the Safety, Efficacy and Pharmacokinetics of PRX167700 in Subjects with Knee Osteoarthritis.

These results have been removed from public view whilst they are reviewed and may need to be corrected before being returned to public view

Summary

EudraCT number	2013-001970-33
Trial protocol	GB
Global end of trial date	28 August 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	167700-002CL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Proximagen Limited
Sponsor organisation address	Minerva Building 250, Babraham Research Campus, Cambridge, United Kingdom, CB22 3AT
Public contact	Clinical Trial Information, Proximagen Limited, 0044 1223 497 300, info@proximagen.com
Scientific contact	Clinical Trial Information, Proximagen Limited, 0044 1223 497 300, info@proximagen.com

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	16 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2014
Global end of trial reached?	Yes
Global end of trial date	28 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of PRX167700 treatment on Pain Intensity after walking and at rest in subjects with moderate to severe pain caused by osteoarthritis (OA) of the knee.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice as required by the International Conference on Harmonisation E6 Guideline. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki and any local regulations and applicable laws were followed appropriately.

Prior to the conduct of any study-related procedures, informed consent was obtained from all subjects. Before obtaining informed consent, information was given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator. Each subject had the opportunity to discuss the study and its alternatives with the Investigator. Subjects were also informed of their right to withdraw from the study at any time.

Background therapy:

Prohibited concomitant therapy:
All analgesic therapy, including over-the-counter pain medications and topical analgesics for OA pain. Medications considered to be analgesics for the treatment of OA pain included non-selective NSAIDs, COX-2 selective NSAIDs, paracetamol, tramadol, and opioid-containing preparations
Oral corticosteroids.
Therapeutic injections into the target knee joint (e. g., corticosteroid and hyaluronic acid).

Other therapies such as methotrexate, gold salts, penicillamine, antimalarials, sulfasalazine, azathioprine, cyclosporine and any anti-inflammatory biological therapy which could be used off-label for the treatment of OA were not permitted. Strong inhibitors of CYP3A4 and CYP2D6 and strong inducers of CYP3A4 were also not permitted.

Permitted concomitant therapy:
Medications, other than the prohibited medications listed above, for the treatment of other underlying diseases or conditions were permitted and were to be maintained at a stable dose during the treatment period, unless a change was medically indicated. All concomitant medications used by the subject at screening (Visit 1), changes to those medications, or introduction of new medications after screening were to be recorded in the electronic consent record form.

Subjects who were taking a stable dose of chondroitin or keratin sulphate, glucosamine, non-specific rubefacients, and nutraceutical products were permitted to continue treatment at the same dose. An established physiotherapy programme could be continued provided it had commenced at least 2 weeks before screening and the session duration or frequency was continued during the study. Low dose aspirin (≤75 mg/day) as prophylactic cardioprotective therapy was also permitted if continued at the same dose.

Rescue medication: Paracetamol (1000 mg) was permitted on an as-needed basis as rescue analgesia during the study, up to a total dose of 4 g per day.

Evidence for comparator:

Not applicable; no comparators were used.

Actual start date of recruitment	09 September 2013
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	United Kingdom: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	24
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject first visit was on 09 September 2013 and the last subject last visit was on 28 August 2014.

Pre-assignment

Screening details:

Screening was performed 7-10 days before start of the treatment period. After screening, eligible subjects were enrolled in a washout period (placebo therapy), and subjects still eligible at the end of this period (7-10 days) were randomised to treatment groups.

Pre-assignment period milestones

Number of subjects started	176[1]
Number of subjects completed	74

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not deemed eligible for randomisation: 102

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 176 subjects entered the washout period, of which 74 eligible subjects were randomised and treated in the treatment period, as planned in the study protocol.

Period 1

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

Blinding implementation details:

The Sponsor and personnel at the study site were blinded to the treatment allocated to individual subjects, except when a medical emergency required knowledge of the treatment randomisation. If the randomisation code for a subject was broken by the study site, the subject was withdrawn from the study and a final assessment completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	PRX167700

Arm description:

Subjects who received PRX167700 400mg 3 times per day.

Arm type	Experimental
Investigational medicinal product name	PRX167700
Investigational medicinal product code	PRX167700
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

PRX167700 400 mg 3 times per day (separated by 6 to 8 hours)

Arm title	Placebo

Arm description:

Subjects who received Placebo taken 3 times per day.

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:

Placebo (lactose capsules) was taken 3 times per day (separated by 6 to 8 hours).

Number of subjects in period 1	PRX167700	Placebo
Started	36	38
Completed	35	35
Not completed	1	3
Adverse event, non-fatal	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	PRX167700
Reporting group description:	
Subjects who received PRX167700 400mg 3 times per day.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received Placebo taken 3 times per day.	

Reporting group values	PRX167700	Placebo	Total
Number of subjects	36	38	74
Age categorical Units: Subjects			
Age continuous			
Subject age			
Units: years arithmetic mean standard deviation	 65.3 ± 7.24	 66.1 ± 6.33	 -
Gender categorical Units: Subjects			
Female	14	18	32
Male	22	20	42
Race Units: Subjects			
White	35	36	71
Asian	1	0	1
Afro-Caribbean	0	1	1
Other	0	1	1
Body mass index Units: kg/square metre arithmetic mean standard deviation	 29.14 ± 3.842	 29.74 ± 3.713	 -
Pain Intensity Assessment Score - Rest			
Pain Intensity at rest at Visit 2 measured using the 11-point numerical rating scale.			
Units: Assessment scale (1-11) arithmetic mean standard deviation	 4.72 ± 1.892	 4.89 ± 1.984	 -
Pain Intensity Assessment Score - Post-walk			
Pain Intensity after walking 100m on a flat course at Visit 2 measured using the 11-point numerical rating scale.			
Units: Assessment scale (1-11) arithmetic mean standard deviation	 6.67 ± 1.549	 7.03 ± 1.619	 -
WOMAC Index (total score)			
Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index completed at Visit 2. The paper questionnaire (5-point Likert scale version) consisted of 3 sections (subscales) assessing pain, stiffness, and difficulty performing daily activities.			

Units: Rating scale			
arithmetic mean	57.91	57.37	
standard deviation	± 11.126	± 11.748	-

End points

End points reporting groups

Reporting group title	PRX167700
Reporting group description:	
Subjects who received PRX167700 400mg 3 times per day.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received Placebo taken 3 times per day.	

Primary: Pain Intensity Assessment Score - Visit 6

End point title	Pain Intensity Assessment Score - Visit 6
End point description:	
The average of the 3 assessments in the target knee joint performed at 1, 2, and 3 hours post-dose. Baseline was the pre-walk (rest) or post-walk value recorded at Visit 2. Change from baseline values are reported.	
End point type	Primary
End point timeframe:	
At specified study visit.	

End point values	PRX167700	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Assessment scale (1-11)				
arithmetic mean (standard deviation)				
Rest	-1.67 (± 2.031)	-0.93 (± 2.135)		
Post-walk	-3.21 (± 2.013)	-2.43 (± 2.188)		

Statistical analyses

Statistical analysis title	Pain intensity at rest - 3 hours post-dose
Comparison groups	PRX167700 v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1242
Method	Mixed models analysis
Parameter estimate	Treatment effect
Point estimate	-0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.49

Notes:

[1] - Mixed effect model with repeated measurement to determine the treatment effect over time.

Statistical analysis title	Pain intensity post-walk - 3 hours post-dose
Comparison groups	PRX167700 v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.153
Method	Mixed models analysis
Parameter estimate	Treatment effect
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

[2] - Mixed effect model with repeated measurement to determine the treatment effect over time.

Primary: Pain Intensity Responder Analysis - Visit 6

End point title	Pain Intensity Responder Analysis - Visit 6[3]

End point description:

Subjects with pain intensity response (percentage decrease from baseline).

End point type	Primary

End point timeframe:

At specified study visit.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Pain intensity response (percentage change from baseline) is displayed showing number of subjects in each category of response. Statistical analysis was performed on pain intensity assessment scores, and is reported under these endpoints.

End point values	PRX167700	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: Number of subjects				
Pre-walk ≥ 30%	20	14		
Pre-walk ≥ 50%	13	11		
Pre-walk ≥ 70%	6	6		
Post-walk ≥ 30%	26	16		

Post-walk ≥ 50%	17	11		
Post-walk ≥ 70%	8	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Total WOMAC Index score

End point title	Total WOMAC Index score

End point description:

Total Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index score.

End point type	Secondary

End point timeframe:

At specified study visit.

End point values	PRX167700	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: Rating scale				
arithmetic mean (standard deviation)				
Visit 6	37.27 (± 18.71)	49.56 (± 16.022)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from the time of signature of informed consent throughout the washout, treatment, and follow-up periods.

Adverse event reporting additional description:

If a subject experienced more than one AE, they were counted once for each system organ class and preferred term.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	PRX167700

Reporting group description:

Subjects treated with PRX167700

Reporting group title	Placebo

Reporting group description:

Subjects receiving placebo

Serious adverse events	PRX167700	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Musculoskeletal and connective tissue disorders			
Lower limb fracture			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	PRX167700	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 36 (38.89%)	21 / 38 (55.26%)	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	

Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Excoriation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 36 (5.56%)	2 / 38 (5.26%)	
occurrences (all)	2	2	
Dizziness			
subjects affected / exposed	1 / 36 (2.78%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Somnolence			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 36 (11.11%)	1 / 38 (2.63%)	
occurrences (all)	4	1	
Abdominal pain			
subjects affected / exposed	3 / 36 (8.33%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	2 / 36 (5.56%)	2 / 38 (5.26%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	1 / 36 (2.78%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Onychoclasis			

subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Viral infection			

subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 36 (2.78%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	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