Clinical trial results:
A Randomised, Parallel Arm, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PRX167700 Added to Existing Non-steroidal Anti-inflammatory Therapy in Adults with Moderate-to-Severe Knee Pain Due to Osteoarthritis

Summary

EudraCT number	2016-001443-39
Trial protocol	GB HU CZ PL ES
Global end of trial date	29 October 2018

Results information

Result version number	v1 (current)
This version publication date	23 October 2019
First version publication date	23 October 2019

Trial information

Trial identification

Sponsor protocol code	167700-004CL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Benevolent AI Cambridge Ltd.
Sponsor organisation address	Minerva Building 250, Babraham Research Campus, Cambridge, United Kingdom, CB22 3AT
Public contact	Clinical Trial Information, Benevolent AI Cambridge Ltd. (formerly Proximagen Ltd.), +44 1223 497 300, jackie.hunter@benevolent.ai
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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	29 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the effect of PRX167700 treatment on knee pain, on a background of stable oral non-steroidal anti-inflammatory drug (NSAID) therapy in subjects with moderate to severe pain caused by osteoarthritis (OA).

Protection of trial subjects:

Independent ethics committees and institutional review boards: The clinical study protocol, informed consent documents, and any other appropriate study-related documents were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB). Protocol amendments for administrative reasons were submitted to the IECs for information only.

Ethical conduct of the study: This study was conducted in accordance with the good clinical practice (GCP) as required by the International Conference on Harmonization (ICH) E6 Guideline for GCP, 1 May 1996 (ICH E6) and ICH E6 (R2), in agreement with the standard operating procedures (SOPs) for clinical investigation and documentation. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki, and any local regulations were followed appropriately. The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines were also followed.

Subject information and informed consent: 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.

Participation in the study and date of informed consent given by the subject was to be documented appropriately in the subject files.

Background therapy:

The patients were on a background of stable NSAID therapy.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	26 January 2017
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	Poland: 48
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Czech Republic: 27

Country: Number of subjects enrolled	Hungary: 44
Worldwide total number of subjects	202
EEA total number of subjects	202

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)	127
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 26 January 2017 & the last subject follow-up was completed on 29 October 2018.

The study was conducted at 30 centres across the UK, Spain, Poland, Hungary & the Czech Republic.

Subjects must have had pain in the target knee for ≥14 days per month in the 3 months preceding screening.

Pre-assignment

Screening details:

The duration per subject was approximately 9 to 12 weeks, including screening (up to 28 days, with a 14-day placebo run-in), treatment (42 days), & follow-up (7 to 10 days) periods. There were 9 study visits.

Subjects who completed the placebo run-in & who still met all of the inclusion criteria & none of the exclusion criteria were randomized.

Period 1

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

Blinding implementation details:

The Interactive Web-Based Response System (IWRS) was programmed with blind breaking instructions. The study blind could be broken if, in the opinion of the investigator, it was in the subject's best interest to know the study treatment assignment. The date and reason that the blind was broken was recorded in the electronic case report form (eCRF).

Arms

Are arms mutually exclusive?	Yes
Arm title	PRX167700

Arm description:

PRX167700 400mg oral tablet three times a day.

Note: The started and completed information refers to the safety population.

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

Dosage and administration details:

One PRX167700 400mg tablet was taken orally three times a day (6-8 hours apart) with water; each dose was taken within 30 minutes after eating. The tablet was uncoated before the study pause, and film-coated after the study pause.

Arm title	Placebo

Arm description:

Placebo oral tablet three times a day.

Arm type	Placebo

Investigational medicinal product name	PRX167700
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One Placebo tablet was taken orally three times a day (6-8 hours apart) with water; each dose was taken within 30 minutes after eating. The tablet was uncoated before the study pause, and film-coated after the study pause.

Number of subjects in period 1	PRX167700	Placebo
Started	101	101
Completed	101	101

Baseline characteristics

Reporting groups	
Reporting group title	PRX167700
Reporting group description:	
PRX167700 400mg oral tablet three times a day. Note: The started and completed information refers to the safety population.	

Reporting group title	Placebo
Reporting group description:	
Placebo oral tablet three times a day.	

Reporting group values	PRX167700	Placebo	Total
Number of subjects	101	101	202
Age categorical			
Subjects were male or female, 50 to 75 years of age, with moderate to severe symptomatic knee OA for at least 3 months before screening, receiving a stable dose of an oral NSAID therapy. Subjects must have had pain in the target knee for ≥14 days per month in the 3 months preceding screening. Subjects who completed the placebo run-in and who still met all of the inclusion criteria and none of the exclusion criteria were randomized on Day 0 (Visit 3) using an IWRS.			
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)	61	66	127
From 65-84 years	40	35	75
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	61.9	62.0	
full range (min-max)	50 to 75	50 to 75	-
Gender categorical			
Units: Subjects			
Female	61	57	118
Male	40	44	84

End points

End points reporting groups

Reporting group title	PRX167700

Reporting group description:

PRX167700 400mg oral tablet three times a day.

Note: The started and completed information refers to the safety population.

Reporting group title	Placebo

Reporting group description:

Placebo oral tablet three times a day.

Primary: WOMAC Pain Score (mITT)

End point title	WOMAC Pain Score (mITT)

End point description:

The primary endpoint was analysed using a MMRM analysis that includes all WOMAC Pain Score changes from baseline through to 6 weeks of treatment. The main comparison was between treatment arms at 6 weeks. Least square mean changes were estimated for PRX167700 and placebo.

End point type	Primary

End point timeframe:

WOMAC Pain Score (mITT) at Visit 8 (Day 42) in mITT population.

Note: The data are presented as LS mean change in WOMAC pain score x 10. These number should be read as - ve numbers.

End point values	PRX167700	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	90		
Units: LS mean change				
LS mean change	42	39		

Statistical analyses

Statistical analysis title	Mixed model repeated measures (MMRM) analysis

Statistical analysis description:

The primary endpoint was analysed using a MMRM analysis that includes all WOMAC Pain Score changes from baseline to 1 week through to 6 weeks. These methods have in recent years become the preferred approach to longitudinal analysis because they utilise the observed data efficiently. Moreover, they naturally handle missing data, if the data are missing at random, in a way that produces unbiased estimates of the treatment effect.

Comparison groups	Placebo v PRX167700

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.563 [2]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.7

Notes:

[1] - For the primary efficacy endpoint, the null (H0) and alternative (H1) hypotheses of the study were as follows:

• H0: PRX167700 and placebo do not differ in their change from baseline in the WOMAC Pain Score at Visit 8 (Day 42).

• H1: PRX167700 and placebo differ in their change from baseline in the WOMAC Pain Score at Visit 8 (Day 42).

[2] - Nil.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were collected throughout the study including the follow-up visit.

Adverse event reporting additional description:

Adverse event information was collected at each study visit.

The information shown below is for Safety Population. The non-serious adverse events with frequency threshold 5% or more are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	PRX167700

Reporting group description:

PRX167700 400mg oral tablet three times a day.

Reporting group title	Placebo

Reporting group description:

Placebo oral tablet three times a day.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious AEs over the 5% threshold for a given preferred term.

In the safety population, the incidence of AEs was similar in both study arms: 40/101 (39.6%) of subjects had AEs during the double blind period in the PRX167700 arm versus 43/101 (42.6%) in the placebo arm. The total number of non-serious AE occurrences in PRX167700 and Placebo arms were 69 and 74 respectively.

Serious adverse events	PRX167700	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 101 (0.99%)	1 / 101 (0.99%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
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			
Tibia fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (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	PRX167700	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 101 (0.00%)	0 / 101 (0.00%)	

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? Yes

Date	Interruption	Restart date
20 March 2017	Recruitment for the study commenced under protocol Version 4. Shortly after starting the study a potential unblinding issue arose concerning the investigational medicinal product (IMP) and an apparent taste difference. Recruitment was paused, and those in the study at the time were withdrawn. The 20 subjects randomized were considered evaluable for safety analysis but unevaluable for the efficacy analysis. At the time of study pause, only UK sites were active.	15 January 2018

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The data under population of trial subjects are for treated subjects. Overall, a total of 520 subjects were enrolled in the study, of which 61.0% were screen failures. A total of 203 subjects were randomised, of which 202 received study drug.

Notes: