Clinical trial results:
A randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy, safety and tolerability of CR4056 administered for 2 weeks in patients with osteoarthritis of the knee with moderate to severe chronic pain

Summary

EudraCT number	2015-001136-37
Trial protocol	GB PL
Global end of trial date	05 July 2016

Results information

Result version number	v1 (current)
This version publication date	30 July 2017
First version publication date	30 July 2017

Trial information

Trial identification

Sponsor protocol code	CR4056-2-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Rottapharm Biotech S.r.l.
Sponsor organisation address	Via Valosa di Sopra 9, Monza, Italy, 20900
Public contact	Lucio Rovati, Rottapharm Biotech S.r.l., +39 0399066104, lucio.rovati@rottapharmbiotech.com
Scientific contact	Lucio Rovati, Rottapharm Biotech S.r.l., +39 0399066104, lucio.rovati@rottapharmbiotech.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	31 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2016
Global end of trial reached?	Yes
Global end of trial date	05 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is the first, proof-of-concept clinical trial of the first-in-class imidazoline-2 ligand CR4056 as an analgesic in humans.
The main objective of the study is to assess the efficacy of CR4056 on pain in patients with knee osteoarthritis (OA) phenotypes.

Protection of trial subjects:

IDMC in charge of periodic review of safety data
Stopping rules based on safety issues

Background therapy:

Paracetamol, as rescue medication

Evidence for comparator:

Not applicable, placebo comparator only - No active comparator was used

Actual start date of recruitment	21 December 2015
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	Poland: 165
Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	213
EEA total number of subjects	213

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)	136
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

165 patients were randomized in Poland and 48 patients were randomized in UK, for a total of 213 patients

Pre-assignment

Screening details:

Patients were selected according to inclusion/exclusion criteria after screening a total of 338 patients (252 in Poland and 86 in UK, respectively). Patients should have had a diagnosis of knee OA at least 6 months before the inclusion and those who were using analgesics should agree to stop them for the whole study duration.

Period 1

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

Blinding implementation details:

Indistinguishable CR4056 and placebo according to randomization

Arms

Are arms mutually exclusive?	Yes
Arm title	CR4056

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	CR4056
Investigational medicinal product code	CR4056
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

14 days of administration - Females 100 mg bid and males 200 mg bid to ensure similar exposure levels due to slight PK gender differences.

Arm title	Placebo

Arm description:

Placebo comparator; 1:2 ratio with active

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:

14 days of administration bid

Number of subjects in period 1	CR4056	Placebo
Started	144	69
Completed	136	63
Not completed	8	6
Consent withdrawn by subject	4	4
Adverse event, non-fatal	4	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period
Reporting group description:	
All patients randomized in the study who received at least one dose of study medication (intention-to-treat)	

Reporting group values	Treatment period	Total	
Number of subjects	213	213	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	136	136	
From 65-84 years	77	77	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	59.9		
standard deviation	± 8.7	-	
Gender categorical			
Units: Subjects			
Female	137	137	
Male	76	76	
BMI			
Body Mass Index, since obesity is a major risk factor for knee OA and a typical disease phenotype. The WHO cut-off BMI for pre-obesity was predetermined in this study (27.5 kg/m2)			
Units: Subjects			
BMI ≥27.5 kg/m2	156	156	
BMI <27.5 kg/m2	57	57	

End points

End points reporting groups	
Reporting group title	CR4056
Reporting group description:	
Active treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo comparator; 1:2 ratio with active	

Primary: Change (EOT vs Baseline) in WOMAC Pain Subscale	
End point title	Change (EOT vs Baseline) in WOMAC Pain Subscale
End point description:	
The WOMAC Pain Subscale (i.e. the first 5 questions of the WOMAC Index questionnaire) is the most widely-used primary outcome measure for knee OA pain.	
End point type	Primary
End point timeframe:	
Baseline to End of Treatment	

End point values	CR4056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	69		
Units: points				
median (full range (min-max))	-16 (-80 to 22)	-10 (-64 to 14)		

Statistical analyses

Statistical analysis title	Comparison (primary) CR4056 vs Placebo
Statistical analysis description:	
This small and short-term proof-of-concept study demonstrated a strong trend for superiority of CR4056 vs placebo in the primary endpoint for pain relief.	
Comparison groups	CR4056 v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)

Secondary: Change (EOT vs Baseline) in WOMAC Pain Subscale Q1	
End point title	Change (EOT vs Baseline) in WOMAC Pain Subscale Q1

End point description:

Question 1 (Q1) – "How much pain do you have walking on a flat surface?" - is the question that better evaluates the impact of an experimental treatment on knee OA pain, and it is widely used as an endpoint in clinical trials.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment

End point values	CR4056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	69		
Units: points				
median (full range (min-max))	-10 (-80 to 30)	0 (-80 to 20)		

Statistical analyses

Statistical analysis title	Comparison (secondary) CR4056 vs Placebo

Statistical analysis description:

The principal secondary analysis on this well validated end point, showed superiority of CR4056 vs placebo in pain control in knee OA.

Comparison groups	CR4056 v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0386
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change (EOT vs Baseline) in WOMAC Pain Subscale in Patients with BMI ≥27.5 kg/m2

End point title	Change (EOT vs Baseline) in WOMAC Pain Subscale in Patients with BMI ≥27.5 kg/m2

End point description:

Primary endpoint analysis on the most prevalent knee OA phenotype in the study (73% of study population)

End point type	Other pre-specified

End point timeframe:

Baseline to End of Treatment

End point values	CR4056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	51		
Units: points				
median (full range (min-max))	-14 (-80 to 22)	0 (-56 to 8)		

Statistical analyses

Statistical analysis title	Comparison CR4056 vs Placebo

Statistical analysis description:

There was a clear superiority of CR4056 vs placebo in the pre-specified analysis of the primary end point conducted in overweight patients, i.e. the most prevalent phenotype in knee OA and in this study.

Comparison groups	CR4056 v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of Informed Consent signature to the end of study visit. In addition, any SAEs the Investigators became aware of at any time after study completion were to be reported to the Sponsor.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	CR4056
Reporting group description:	
Active treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo comparator; 1:2 ratio with active	

Serious adverse events	CR4056	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 144 (0.00%)	0 / 69 (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: 3 %

Non-serious adverse events	CR4056	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 144 (41.67%)	23 / 69 (33.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 144 (13.89%)	5 / 69 (7.25%)	
occurrences (all)	25	7	
Somnolence			
subjects affected / exposed	7 / 144 (4.86%)	3 / 69 (4.35%)	
occurrences (all)	7	3	
Dizziness			

subjects affected / exposed	4 / 144 (2.78%)	3 / 69 (4.35%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 144 (2.08%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	5 / 144 (3.47%)	1 / 69 (1.45%)	
occurrences (all)	5	1	
Nausea			
subjects affected / exposed	3 / 144 (2.08%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	3 / 144 (2.08%)	0 / 69 (0.00%)	
occurrences (all)	3	0	
Skin burning sensation			
subjects affected / exposed	2 / 144 (1.39%)	0 / 69 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 144 (2.78%)	1 / 69 (1.45%)	
occurrences (all)	4	1	
Urinary tract infection			
subjects affected / exposed	3 / 144 (2.08%)	1 / 69 (1.45%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 144 (2.08%)	1 / 69 (1.45%)	
occurrences (all)	3	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