# 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