# Clinical trial results:
# A randomised, double-blind, placebo controlled, parallel group, multi-centre, study to evaluate the efficacy, safety, tolerability and pharmacokinetics of ONO-4474 in patients with pain due to osteoarthritis of the knee

## Summary

| | |
|---|---|
| EudraCT number | 2016-002675-97 |
| Trial protocol | HU DK ES PL GB |
| Global end of trial date | 09 January 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 December 2018 |
| First version publication date | 07 December 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ONO-4474-02 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02997696 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Ono Pharmaceutical Co. Ltd. |
| Sponsor organisation address | 8-2, Kyutaromachi 1-chome, Chuo-ku, Osaka, Japan, |
| Public contact | Clinical Trial Information Desk, Ono Pharma UK Ltd, 44 207421 4920, ctinfo@ono-uk.co.uk |
| Scientific contact | Clinical Trial Information Desk, Ono Pharma UK Ltd, 44 207421 4920, ctinfo@ono-uk.co.uk |

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 | 13 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 January 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Investigate the effects of ONO-4474 on walking pain

Protection of trial subjects:

Before they were screened for the study, all subjects read the informed consent form, which contained information about the study design, investigational product, procedures, and risks. The investigator, or physician designated by the investigator, explained the benefits and risks of participation in the study to each subject, and obtained written informed consent before the subject entered the study. In obtaining and documenting informed consent, the investigator was required to comply with the applicable regulatory requirements and adhere to ICH-GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Each subject was free to withdraw from the study at any time without giving reasons.

Rescue medication was permitted. Subjects were willing to discontinue use of all analgesic pharmacotherapy (aside from rescue medication) from Visit 2 to randomisation (Visit 3) and for the duration of the treatment and follow-up periods (Visit 8).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 February 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: 40 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Worldwide total number of subjects | 70 |
| EEA total number of subjects | 70 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| 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) | 37 |
| From 65 to 84 years | 33 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was terminated early due to non-safety reasons.

### Pre-assignment

Screening details:

247 of the 317 screened subjects failed screening, mostly due to not meeting inclusion/exclusion criteria (221 patients). Following screening (Visit 1), eligible patients entered a washout period (minimum 1 week) during which previous medications for OA analgesia were stopped (Visit 2). Randomization was performed at Visit 3 (Week 0; Baseline).

### 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 |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Placebo BID, 12 hours apart

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablets were to be administered orally BID with water, immediately following a meal, at approximately 12-hour intervals, where possible. At Visit 3 (randomization visit), only the evening dose was to be taken and at Visit 7 (Week 4), only the morning dose was to be taken. At Visits 4 (Week 1), 5 (Week 2) and 7 (Week 4) the morning dose was to be taken at the study site, where a standard breakfast was provided. A combination of four tablets, either ONO-4474 or matching placebo, were to be administered on each dosing occasion (two tablets from each of the two bottles dispensed). At Visit 7, (Week 4) patients were to take the morning dose and then return all remaining study drug to site staff. No treatment was to be administered at Visit 6 (Week 3); this was a telephone call.

| | |
|---|---|
| **Arm title** | ONO-4474 100 mg |

Arm description:

ONO-4474 100 mg BID, 12 hours apart

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4474 100 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ONO-4474, containing 50 mg of the free form of ONO-4474 TS (toluenesulfonate), was to be administered orally BID with water, immediately following a meal, at approximately 12-hour intervals, where possible. At Visit 3 (randomization visit), only the evening dose was to be taken and at Visit 7 (Week 4), only the morning dose was to be taken. At Visits 4 (Week 1), 5 (Week 2) and 7 (Week 4) the morning dose was to be taken at the study site, where a standard breakfast was provided. A combination of four tablets, either ONO-4474 or matching Placebo, were to be administered on each

dosing occasion (two tablets from each of the two bottles dispensed). At Visit 7, (Week 4) patients were to take the morning dose and then return all remaining study drug to site staff. No treatment was to be administered at Visit 6 (Week 3); this was a telephone call.

| **Arm title** | ONO-4474 200 mg |
|---|---|
| Arm description: | |
| ONO-4474 200 mg BID, 12 hours apart | |
| Arm type | Experimental |
| Investigational medicinal product name | ONO-4474 200 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

ONO-4474, containing 50 mg of the free form of ONO-4474 TS (toluenesulfonate), was to be administered orally BID with water, immediately following a meal, at approximately 12-hour intervals, where possible. At Visit 3 (randomization visit), only the evening dose was to be taken and at Visit 7 (Week 4), only the morning dose was to be taken. At Visits 4 (Week 1), 5 (Week 2) and 7 (Week 4) the morning dose was to be taken at the study site, where a standard breakfast was provided. A combination of four tablets, either ONO-4474 or matching Placebo, were to be administered on each dosing occasion (two tablets from each of the two bottles dispensed). At Visit 7, (Week 4) patients were to take the morning dose and then return all remaining study drug to site staff. No treatment was to be administered at Visit 6 (Week 3); this was a telephone call.

| **Number of subjects in period 1** | Placebo | ONO-4474 100 mg | ONO-4474 200 mg |
|---|---|---|---|
| Started | 21 | 23 | 26 |
| Completed | 18 | 20 | 22 |
| Not completed | 3 | 3 | 4 |
| Consent withdrawn by subject | - | 1 | - |
| Violation of eligibility | 1 | - | - |
| Adverse event, non-fatal | 2 | 2 | 2 |
| Intake of prohibited medications | - | - | 1 |
| Other (no further explanation) | - | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo BID, 12 hours apart | |
| Reporting group title | ONO-4474 100 mg |
| Reporting group description: | |
| ONO-4474 100 mg BID, 12 hours apart | |
| Reporting group title | ONO-4474 200 mg |
| Reporting group description: | |
| ONO-4474 200 mg BID, 12 hours apart | |

| Reporting group values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg |
|---|---|---|---|
| Number of subjects | 21 | 23 | 26 |
| 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) | 8 | 14 | 15 |
| From 65-84 years | 13 | 9 | 11 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 64.6 | 62.2 | 61.5 |
| standard deviation | ± 6.3 | ± 6.7 | ± 7.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 15 | 12 | 18 |
| Male | 6 | 11 | 8 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 70 | | |
| 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) | 37 | | |

| | | | |
|---|---|---|---|
| From 65-84 years | 33 | | |
| 85 years and over | 0 | | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 45 | | |
| Male | 25 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set will comprise all randomised patients who had at least one dose of study drug and at least one valid post baseline efficacy endpoint.

| **Reporting group values** | Full analysis set | | |
|---|---|---|---|
| Number of subjects | 70 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | 37 | | |
| From 65-84 years | 33 | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62.7 | | |
| standard deviation | ± 6.8 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 45 | | |
| Male | 25 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: Placebo BID, 12 hours apart | |
| Reporting group title | ONO-4474 100 mg |
| Reporting group description: ONO-4474 100 mg BID, 12 hours apart | |
| Reporting group title | ONO-4474 200 mg |
| Reporting group description: ONO-4474 200 mg BID, 12 hours apart | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The full analysis set will comprise all randomised patients who had at least one dose of study drug and at least one valid post baseline efficacy endpoint. | |

### Primary: Change from Baseline in Mean Daily Average Index Knee Pain While Walking (24h recall) by Week, up to Week 4

| | |
|---|---|
| End point title | Change from Baseline in Mean Daily Average Index Knee Pain While Walking (24h recall) by Week, up to Week 4 |
| End point description: | |
| End point type | Primary |
| End point timeframe: Baseline to Week 4 | |

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: Knee pain score | | | | |
| arithmetic mean (standard deviation) | -18.34 (± 23.34) | -21.92 (± 18.68) | -29.94 (± 22.06) | |

### Statistical analyses

| Statistical analysis title | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.841 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.39 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.21 |
| upper limit | 12.44 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.315 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.2 |
| upper limit | 6.62 |

## Secondary: Change from Baseline in Mean Daily Average Index Knee Pain While Walking (24h Recall) at Week 4, up to Follow-up Week 2

| End point title | Change from Baseline in Mean Daily Average Index Knee Pain While Walking (24h Recall) at Week 4, up to Follow-up Week 2 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change from baseline to Week 4, Follow-up Week 1 and Follow-up Week 2

| **End point values** | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19[1] | 21[2] | 24[3] | |
| Units: Knee pain score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Baseline to Week 4 | -19.41 (± 23.08) | -21.21 (± 18.60) | -27.95 (± 22.99) | |
| Change from Baseline to Follow-up Week 1 | -19.24 (± 23.64) | -17.52 (± 14.77) | -18.66 (± 26.45) | |
| Change from Baseline to Follow-up Week 2 | -19.83 (± 25.73) | -14.42 (± 11.92) | -21.28 (± 20.61) | |

Notes:
[1] - n=19 at Week 4, n=19 at Follow-up Week 1, n=17 at Follow-up Week 2.
[2] - n=21 at Week 4, n=20 at Follow-up Week 1, n=20 at Follow-up Week 2.
[3] - n=24 at Week 4, n=23 at Follow-up Week 1, n=22 at Follow-up Week 2.

### Statistical analyses

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Change from baseline to Week 4 | |
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.873 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.78 |
| upper limit | 15.02 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Change from baseline to Week 4 | |
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.471 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.41 |
| upper limit | 8.61 |

## Secondary: Change from Baseline in WOMAC Walking Pain (Q1), Pain (Q1-Q5), Stiffness (Q6-Q7), and Physical Function (Q8-Q24) Scores (48h Recall)

| End point title | Change from Baseline in WOMAC Walking Pain (Q1), Pain (Q1-Q5), Stiffness (Q6-Q7), and Physical Function (Q8-Q24) Scores (48h Recall) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
Baseline to Week 4

| **End point values** | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: WOMAC score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Walking pain score (Q1) | -2.50 (± 2.20) | -2.50 (± 1.99) | -3.45 (± 2.50) | |
| Pain score (Q1-Q5) | -2.22 (± 2.28) | -2.54 (± 2.06) | -3.48 (± 2.49) | |
| Stiffness score (Q6-Q7) | -1.33 (± 1.96) | -2.45 (± 2.46) | -3.50 (± 3.00) | |
| Physical function score (Q8-Q24) | -2.04 (± 2.30) | -2.70 (± 2.03) | -3.28 (± 2.22) | |

**Statistical analyses**

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Walking pain | |
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.884 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.27 |
| upper limit | 1.48 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Pain | |
| Comparison groups | Placebo v ONO-4474 100 mg |

| | |
|---|---|
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.938 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.45 |
| upper limit | 1.34 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Statistical analysis description: Stiffness | |
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.323 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.17 |
| upper limit | 0.73 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Statistical analysis description: Physical function | |
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.685 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.59 |
| upper limit | 1.05 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Walking pain | |
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.247 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.13 |
| upper limit | 0.56 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Pain | |
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.175 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.31 |
| upper limit | 0.43 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Stiffness | |
| Comparison groups | Placebo v ONO-4474 200 mg |

| | |
|---|---|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.013 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.23 |
| upper limit | -0.4 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Statistical analysis description:<br>Physical function | |
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.176 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.18 |
| upper limit | 0.41 |

## Secondary: Change from Baseline in Mean Daily Average Index Knee Pain (24h Recall) at Week 4

| End point title | Change from Baseline in Mean Daily Average Index Knee Pain (24h Recall) at Week 4 |
|---|---|
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe:<br>Baseline to Week 4 | |

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: Knee pain score | | | | |
| arithmetic mean (standard deviation) | -17.99 (± 21.88) | -23.08 (± 18.79) | -32.81 (± 23.13) | |

**Statistical analyses**

| Statistical analysis title | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.764 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.68 |
| upper limit | 11.56 |

| Statistical analysis title | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.173 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.3 |
| upper limit | 4.1 |

**Secondary: Change from Baseline in Patient Global Assessment by Week, up to Follow-up Visit**

| End point title | Change from Baseline in Patient Global Assessment by Week, up to Follow-up Visit |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change from Baseline to Follow-up Visit

| **End point values** | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: Patient Global Assessment Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline to Week 4 | -17.83 (± 23.79) | -25.20 (± 17.08) | -36.41 (± 25.28) | |

**Statistical analyses**

| **Statistical analysis title** | LS Mean Difference ONO-4474 100 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 100 mg |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.891 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.1 |
| upper limit | 12.28 |

| **Statistical analysis title** | LS Mean Difference ONO-4474 200 mg vs Placebo |
|---|---|
| Comparison groups | Placebo v ONO-4474 200 mg |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.079 |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.7 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.79 |
| upper limit | 1.4 |

## Secondary: Change from Baseline in Clinical Global Impression by Week, up to Follow-up Visit

| End point title | Change from Baseline in Clinical Global Impression by Week, up to Follow-up Visit |
|---|---|

End point description:

Change from Baseline to Week 4 is presented.

| End point type | Secondary |
|---|---|

End point timeframe:

Change from Baseline to Follow-up Visit

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 | 23 | 26 | |
| Units: Number of patients | | | | |
| Any improvement | 12 | 19 | 20 | |
| Very much improved | 3 | 1 | 5 | |
| Much improved | 4 | 11 | 10 | |
| Minimally improved | 5 | 7 | 5 | |
| No change | 4 | 0 | 2 | |
| Any worsening | 2 | 1 | 0 | |
| Minimally worse | 2 | 1 | 0 | |
| Much worse | 0 | 0 | 0 | |
| Very much worse | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: EuroQoL EQ-5D-5L Five Domains from Baseline to Week 4

| End point title | EuroQoL EQ-5D-5L Five Domains from Baseline to Week 4 |
|---|---|

End point description:

The proportion of patients with favourable shifts in the EuroQoL EQ-5D-5L domains (mobility, self-care, usual activity, pain or discomfort, anxiety or depression) was generally greater in the ONO-4474 treatment groups compared to placebo.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Week 4

| End point values | Full analysis set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: Number of patients | 70 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Rescue Medication for OA Symptoms

| End point title | Rescue Medication for OA Symptoms |
|---|---|

End point description:

There was no clear difference between treatment groups in use of rescue medication and the time to first use of rescue medication for OA symptoms.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Follow-up visit

| End point values | Full analysis set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: Number of patients | 70 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pre-Dose Plasma Concentration (ng/mL) of ONO-4474 by Week

| End point title | Pre-Dose Plasma Concentration (ng/mL) of ONO-4474 by Week |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 1 to Week 4

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[4] | 20[5] | 24[6] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 | () | 27.755 (± 21.373) | 77.347 (± 80.061) | |
| Week 2 | () | 25.579 (± 25.231) | 80.932 (± 120.372) | |
| Week 4 | () | 21.218 (± 16.238) | 64.209 (± 95.117) | |

Notes:

[4] - Not applicable; PK could not be assessed in patients receiving placebo

[5] - Pharmacokinetic analysis set (n=15 at Week 1, n=19 at Week 2, n=18 at Week 4)

[6] - Pharmacokinetic analysis set (n=17 at Week 1, n=22 at Week 2, n=22 at Week 4)

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: OMERACT-OARSI Responders

| End point title | OMERACT-OARSI Responders |
|---|---|
| End point description:<br>Data presented for Week 4 | |
| End point type | Other pre-specified |
| End point timeframe:<br>Week 1, Week 2, Week 4 | |

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: percent | | | | |
| number (not applicable) | 44.4 | 70.0 | 86.4 | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Proportional Changes of Mean Daily Walking Pain Score by Improvement Rate (30%, 50%, and 70%) at Week 4

| End point title | Proportional Changes of Mean Daily Walking Pain Score by Improvement Rate (30%, 50%, and 70%) at Week 4 |
|---|---|
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe:<br>Week 4 | |

| End point values | Placebo | ONO-4474 100 mg | ONO-4474 200 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 20 | 22 | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| ≥ 30% decrease | 44.4 | 55.0 | 54.5 | |
| ≥ 50% decrease | 22.2 | 25.0 | 54.5 | |
| ≥ 70% decrease | 11.1 | 15.0 | 27.3 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At all visits from Screening (Visit 1) to follow-up (Visit 8)

Adverse event reporting additional description:

Data for the number of occurrences of each TEAE were not collected as the study was not designed to collect for the number of events in each subject group. Therefore, the number of occurrences of each TEAE have been reported as 0.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Only treatment-emergent AEs are reported.

| | |
|---|---|
| Reporting group title | ONO-4474 100 mg |

Reporting group description:

Only treatment-emergent AEs are reported.

| | |
|---|---|
| Reporting group title | ONO-4474 200 mg |

Reporting group description:

Only treatment-emergent AEs are reported.

| | |
|---|---|
| Reporting group title | Total |

Reporting group description:

Only treatment-emergent AEs are reported.

| Serious adverse events | Placebo | ONO-4474 100 mg | ONO-4474 200 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 1 / 26 (3.85%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Total | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Placebo | ONO-4474 100 mg | ONO-4474 200 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 21 (47.62%) | 17 / 23 (73.91%) | 19 / 26 (73.08%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 23 (8.70%) | 3 / 26 (11.54%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 2 / 26 (7.69%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 2 / 26 (7.69%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 3 / 26 (11.54%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 5 / 26 (19.23%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 3 / 26 (11.54%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 23 (4.35%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 23 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Total | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 70 (65.71%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 0 | | |
| Pharyngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 March 2017 | Amendment No.02. Global substantial amendment of the protocol to provide clarification on inclusion criterion #2 relating to the definition of females of non-child-bearing potential. To allow investigator sites to re-screen patients in limited circumstances, judged on a case by case basis, following approval by Medical Monitor. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 16 October 2017 | Early termination of the study. | - |

Notes:

### Limitations and caveats

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

| |
|---|
| Due to the small sample size as a result of early study discontinuation, it is not possible to reach a definitive conclusion regarding the efficacy and safety of ONO-4474 in Study ONO-4474-02. |

Notes: