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: 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: 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: 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: 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: 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: 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: 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: 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: 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: Data presented for Week 4	
End point type	Other pre-specified
End point timeframe: 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: 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: