



Clinical trial results:

A randomised, double-blind, parallel group, multiple-dose 3 month study of ibuprofen 400mg alone, paracetamol (acetaminophen) 1000mg alone, ibuprofen 200mg plus paracetamol 500mg and ibuprofen 400mg plus paracetamol 1000mg, all taken three times daily, in community patients with chronic knee pain.

Summary

EudraCT number	2006-005668-21
Trial protocol	GB
Global end of trial date	27 May 2008

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019

Trial information

Trial identification

Sponsor protocol code	NL0605
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Reckitt Benckiser Healthcare International Ltd
Sponsor organisation address	Dansom Lane, Hull, United Kingdom, HU8 7DS
Public contact	Clinical Research, Clinical Research Director, clinicalrequests@rb.com
Scientific contact	Clinical Research, Clinical Research Director, clinicalrequests@rb.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	08 October 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2008
Global end of trial reached?	Yes
Global end of trial date	27 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to demonstrate the overall effectiveness (balance of efficacy and tolerability) of a combination of ibuprofen and acetaminophen in community patients with chronic knee pain.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice(GCP) and the ethical principles contained within the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2007
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	United Kingdom: 892
Worldwide total number of subjects	892
EEA total number of subjects	892

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)	562
From 65 to 84 years	330
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicentre trial, involving eight sites.

Pre-assignment

Screening details:

A total of 1079 subjects were screened for the study; 187 subjects were screen failures. 892 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Reference: Ibu 400mg

Arm description:

Ibuprofen 400mg (2 x 200mg), caplets by mouth three times daily

Arm type	Active comparator
Investigational medicinal product name	Nurofen 200mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 400mg (2 x 200mg), caplets by mouth three times daily

Arm title	Reference: Para 1000mg
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Arm description:

Paracetamol 1000mg (2 x 500mg), caplets by mouth three times daily

Arm type	Active comparator
Investigational medicinal product name	Panafen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Paracetamol 1000mg (2 x 500mg), caplets by mouth three times daily

Arm title	Test: Ibu 200mg + Para 500mg
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Arm description:

Fixed combination ibuprofen 200mg and paracetamol 500mg, tablet by mouth three times daily

Arm type	Experimental
Investigational medicinal product name	ibuprofen 200mg and paracetamol 500mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fixed combination ibuprofen 200mg and paracetamol 500mg, tablet by mouth three times daily

Arm title	Test: Ibu 400mg + Para 1000mg
Arm description: Ibuprofen 400mg and paracetamol 1000mg (2x200mg ibuprofen plus 2x500mg paracetamol), tablet by mouth three times daily	
Arm type	Experimental
Investigational medicinal product name	ibuprofen 400mg and paracetamol 1000mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 400mg and paracetamol 1000mg (2x200mg ibuprofen plus 2x500mg paracetamol), tablet by mouth three times daily

Number of subjects in period 1	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg
Started	224	222	222
Completed	163	136	155
Not completed	61	86	67
Adverse events	31	37	29
Lost to follow-up	4	5	2
Protocol violation	-	2	4
Death/serious Adverse event	1	2	-
Insufficient pain relief	13	22	13
Investigator decision	3	1	1
Other reason	1	4	4
Withdraw consent	8	13	14

Number of subjects in period 1	Test: Ibu 400mg + Para 1000mg
Started	224
Completed	161
Not completed	63
Adverse events	37
Lost to follow-up	4
Protocol violation	-
Death/serious Adverse event	1
Insufficient pain relief	11

Investigator decision	-
Other reason	-
Withdraw consent	10

Baseline characteristics

Reporting groups

Reporting group title	Reference: Ibu 400mg
Reporting group description: Ibuprofen 400mg (2 x 200mg), caplets by mouth three times daily	
Reporting group title	Reference: Para 1000mg
Reporting group description: Paracetamol 1000mg (2 x 500mg), caplets by mouth three times daily	
Reporting group title	Test: Ibu 200mg + Para 500mg
Reporting group description: Fixed combination ibuprofen 200mg and paracetamol 500mg, tablet by mouth three times daily	
Reporting group title	Test: Ibu 400mg + Para 1000mg
Reporting group description: Ibuprofen 400mg and paracetamol 1000mg (2x200mg ibuprofen plus 2x500mg paracetamol), tablet by mouth three times daily	

Reporting group values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg
Number of subjects	224	222	222
Age categorical			
Units: Subjects			
18-64	139	130	148
65-84	85	92	74
Age continuous			
Units: years			
arithmetic mean	60.8	61.6	60.1
standard deviation	± 9.8	± 10.5	± 10.2
Gender categorical			
Units: Subjects			
Female	124	99	115
Male	100	123	107
Height			
Units: cm			
arithmetic mean	167.4	167.4	167.8
standard deviation	± 9.6	± 9.4	± 9.1
Weight			
Units: kg			
arithmetic mean	83.6	85.4	85.7
standard deviation	± 18.4	± 17.5	± 17.9
BMI			
BMI - Body Mass Index			
Units: kg/m2			
arithmetic mean	29.8	30.4	30.4
standard deviation	± 5.7	± 5.4	± 5.8
Reporting group values	Test: Ibu 400mg + Para 1000mg	Total	
Number of subjects	224	892	

Age categorical Units: Subjects			
18-64	145	562	
65-84	79	330	
Age continuous Units: years			
arithmetic mean	59.9		
standard deviation	± 10.2	-	
Gender categorical Units: Subjects			
Female	99	437	
Male	125	455	
Height Units: cm			
arithmetic mean	169.1		
standard deviation	± 8.9	-	
Weight Units: kg			
arithmetic mean	85.1		
standard deviation	± 17.0	-	
BMI			
BMI - Body Mass Index			
Units: kg/m ²			
arithmetic mean	29.8		
standard deviation	± 5.8	-	

End points

End points reporting groups

Reporting group title	Reference: Ibu 400mg
Reporting group description: Ibuprofen 400mg (2 x 200mg), caplets by mouth three times daily	
Reporting group title	Reference: Para 1000mg
Reporting group description: Paracetamol 1000mg (2 x 500mg), caplets by mouth three times daily	
Reporting group title	Test: Ibu 200mg + Para 500mg
Reporting group description: Fixed combination ibuprofen 200mg and paracetamol 500mg, tablet by mouth three times daily	
Reporting group title	Test: Ibu 400mg + Para 1000mg
Reporting group description: Ibuprofen 400mg and paracetamol 1000mg (2x200mg ibuprofen plus 2x500mg paracetamol), tablet by mouth three times daily	

Primary: Change from baseline in Mean WOMAC OA index pain subscale scores

End point title	Change from baseline in Mean WOMAC OA index pain subscale scores
End point description: Full analysis set consisted of all patients who were randomised to the study and who received at least one dose of study medication, i.e. the intent-to-treat population. Any patients with treatment administration errors were analysed according to the treatment to which they were randomised. WOMAC OA Index sub-scale for pain normalised to 0-100mm scale, a lower score is favourable WOMAC - Western Ontario McMaster Universities Osteoarthritis Index OA - Osteoarthritis	
End point type	Primary
End point timeframe: At Day 1 (Baseline) and Day 10.	

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N=193, 188, 201, 204)	43.8 (± 14.8)	43.2 (± 14.4)	45.0 (± 16.4)	42.4 (± 15.8)
Change from baseline (N = 193, 188, 201, 204)	-13.3 (± 17.8)	-10.1 (± 16.3)	-12.8 (± 16.7)	-15.0 (± 17.5)

Statistical analyses

Statistical analysis title	WOMAC OA - Ibu 400mg + Para 1000mg vs Para 1000mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Reference: Para 1000mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0012
Method	ANCOVA

Statistical analysis title	WOMAC OA - Ibu 200mg + Para 500mg vs Para 1000mg
Comparison groups	Reference: Para 1000mg v Test: Ibu 200mg + Para 500mg
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1389
Method	ANCOVA

Statistical analysis title	WOMAC OA - Ibu 400mg + Para 1000mg vs Ibu 400mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Reference: Ibu 400mg
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1787
Method	ANCOVA

Statistical analysis title	WOMAC OA - Ibu 200mg + Para 500mg vs Ibu 400mg
Comparison groups	Test: Ibu 200mg + Para 500mg v Reference: Ibu 400mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6772
Method	ANCOVA

Statistical analysis title	WOMAC - Ibu400mg+Para1000mg vs Ibu200mg+Para500mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Test: Ibu 200mg + Para 500mg

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0756
Method	ANCOVA

Primary: Number of subjects with Patient global assessment of treatment (LOCF)

End point title	Number of subjects with Patient global assessment of treatment (LOCF)
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End point description:

The patient global assessment (assessed by 5-point Likert scale) was recorded on a five-point scale where 1 = Excellent, 2 = Good, 3 = Fair, 4 = Poor and 5 = Unacceptable, in response to the question.

LOCF - last observation carried forward

Full analysis dataset

End point type	Primary
End point timeframe:	At Day 10, Week 7 and Week 13.

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: Number of subjects				
1 Excellent (N = 219, 220, 220, 221)	44	29	39	51
2 Good (N = 219, 220, 220, 221)	67	71	80	82
3 Fair (N = 219, 220, 220, 221)	54	43	42	37
4 Poor (N = 219, 220, 220, 221)	37	45	42	35
5 Unacceptable (N = 219, 220, 220, 221)	17	32	17	16

Statistical analyses

Statistical analysis title	Patient Global-Ibu400mg + Para1000mg vs Para1000mg
Comparison groups	Reference: Para 1000mg v Test: Ibu 400mg + Para 1000mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0002
Method	ANCOVA

Statistical analysis title	Patient Global-Ibu400mg + Para1000mg vs Ibu 400mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Reference: Ibu 400mg
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2243
Method	ANCOVA

Statistical analysis title	Patient Global-Ibu200mg + Para500mg vs Para1000mg
Comparison groups	Test: Ibu 200mg + Para 500mg v Reference: Para 1000mg
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0152
Method	ANCOVA

Statistical analysis title	Patient Global-Ibu200mg + Para500mg vs Ibu400mg
Comparison groups	Test: Ibu 200mg + Para 500mg v Reference: Ibu 400mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9539
Method	ANCOVA

Primary: Mean person days exposure with incidence of Moderate and Severe adverse events regardless to treatment relationship

End point title	Mean person days exposure with incidence of Moderate and Severe adverse events regardless to treatment relationship
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End point description:

Intensity was determined by the Investigator. For symptomatic AEs the following definitions were applied.

Moderate =The AE results in some limitation of usual activities; the subject may experience significant discomfort.

Severe = The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Full analysis set

End point type	Primary
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End point timeframe:

At Day 10, Week 7, Week 13 and Endpoint (LOCF)

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: number of subjects				
arithmetic mean (standard deviation)	6.7 (± 28.7)	3.9 (± 7.9)	4.0 (± 10.0)	5.2 (± 12.8)

Statistical analyses

Statistical analysis title	AEs - Ibu 400mg + Para 1000mg vs Para 1000mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Reference: Para 1000mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	log-linear ratio
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.56

Statistical analysis title	AEs - Ibu 200mg + Para 500mg vs Para 1000mg
Comparison groups	Test: Ibu 200mg + Para 500mg v Reference: Para 1000mg
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	log-linear ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.39

Statistical analysis title	AEs - Ibu400mg+Para1000mg vs Ibu200mg+Para500mg
Comparison groups	Test: Ibu 400mg + Para 1000mg v Test: Ibu 200mg + Para 500mg

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	log-linear ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.42

Statistical analysis title	AEs - Ibu 400mg + Para 1000mg vs Ibu 400mg
Comparison groups	Reference: Ibu 400mg v Test: Ibu 400mg + Para 1000mg
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	log-linear ratio
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.73

Statistical analysis title	AEs - Ibu 200mg + Para 500mg vs Ibu 400mg
Comparison groups	Test: Ibu 200mg + Para 500mg v Reference: Ibu 400mg
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	log-linear ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.55

Secondary: Number of subjects with Acceptability of knee pain in the last 48 hours

End point title	Number of subjects with Acceptability of knee pain in the last 48 hours
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End point description:

Knee pain in the last 48 hours by asking question "Thinking only of the pain you felt in your knee during the last 48 hours, if you were to remain with that pain for the rest of your life would that be acceptable to you?" (Yes/No)

full analysis set

LOCF - Last observation carried forward

End point type	Secondary
End point timeframe:	
At Day 10, Week 7, Week 13 and Endpoint (LOCF)	

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: Number of subjects				
Pain acceptable-Yes at Baseline(N=224,222,222,224)	83	80	71	85
Pain acceptable - Yes at Day 10(N=195,195,203,205)	125	119	115	151
Pain acceptable - Yes at Week 7(N=174,149,158,177)	118	108	109	133
Pain acceptable -Yes at Week 13(N=160,134,152,160)	113	95	116	119
Pain acceptable-Yes at Endpoint(N=217,219,220,222)	139	138	141	144

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Mean WOMAC Pain in the signal knee

End point title	Change from baseline in Mean WOMAC Pain in the signal knee
End point description:	
WOMAC OA Index sub-scale for pain normalised to 0-100mm scale, a lower score is favourable	
Full analysis set	
End point type	Secondary
End point timeframe:	
At week 7, week 13 and Endpoint (LOCF)	

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N = 224, 222, 222, 224)	44.0 (± 15.2)	43.0 (± 14.9)	45.0 (± 16.0)	42.5 (± 15.7)
Change from baseline at Week 7(N=174,148,161,173)	-15.0 (± 19.7)	-14.7 (± 17.8)	-17.1 (± 18.8)	-18.0 (± 20.3)

Change from baseline at Week 13(N=162,136,151,159)	-17.6 (± 19.6)	-15.9 (± 16.3)	-16.8 (± 19.0)	-18.3 (± 19.5)
Change from baseline Endpoint(N=217,215,220,218)	-13.3 (± 20.7)	-10.8 (± 18.6)	-14.7 (± 18.7)	-15.5 (± 20.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean WOMAC subscale for physical function in the signal knee

End point title	Change from baseline in mean WOMAC subscale for physical function in the signal knee
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End point description:

WOMAC OA Index sub-scale for pain normalised to 0-100mm scale, a lower score is favourable

Full analysis set

End point type	Secondary
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End point timeframe:

At Day 10, Week 7, Week 13 and Endpoint (LOCF)

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N = 224, 222, 222, 224)	42.8 (± 18.5)	42.7 (± 18.9)	43.1 (± 19.7)	41.6 (± 19.1)
Change from baseline at Day 10(N=186,186,194,203)	-10.8 (± 14.3)	-8.3 (± 15.5)	-10.3 (± 14.8)	-13.1 (± 16.5)
Change from baseline at Week 7(N=170,145,154,171)	-13.1 (± 17.0)	-11.2 (± 16.8)	-14.1 (± 16.2)	-16.0 (± 19.1)
Change from baseline at Week 13(N=158,133,144,156)	-13.0 (± 17.1)	-12.7 (± 17.2)	-13.4 (± 18.2)	-14.5 (± 18.5)
Change from baseline at Endpoint(N=213,211,216,217)	-10.5 (± 17.8)	-9.2 (± 17.8)	-10.9 (± 17.4)	-12.5 (± 18.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean WOMAC subscale for Joint stiffness

End point title	Change from baseline in mean WOMAC subscale for Joint stiffness
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End point description:

WOMAC OA Index sub-scale for pain normalised to 0-100mm scale, a lower score is favourable.

Full analysis set

End point type Secondary

End point timeframe:

At Day 10, Week 7, Week 13 and Endpoint (LOCF)

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N = 224, 222, 222, 224)	54.4 (± 19.8)	51.4 (± 21.0)	54.1 (± 22.4)	52.4 (± 21.7)
Change from baseline at Day 10(N=193,194,202,206)	-17.3 (± 20.8)	-10.7 (± 20.5)	-16.4 (± 21.1)	-18.3 (± 21.2)
Change from baseline at Week 7(N=174,147,160,173)	-20.8 (± 21.9)	-16.4 (± 21.7)	-21.7 (± 24.1)	-23.1 (± 23.6)
Change from baseline at Week 13(N=161,135,152,159)	-22.6 (± 22.8)	-17.0 (± 23.3)	-22.0 (± 25.9)	-23.3 (± 25.6)
Change from baseline at Endpoint(N=217,218,219,217)	-17.2 (± 24.0)	-12.8 (± 23.7)	-18.2 (± 25.1)	-19.4 (± 25.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean WOMAC Composite score

End point title Change from baseline in mean WOMAC Composite score

End point description:

WOMAC OA Index sub-scale for pain normalised to 0-100mm scale, a lower score is favourable

Full analysis set

End point type Secondary

End point timeframe:

At Day 10, Week 7, Week 13 and Endpoint (LOCF)

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N = 224, 222, 222, 224)	44.1 (± 16.6)	43.5 (± 16.9)	44.2 (± 17.9)	42.7 (± 17.4)
Change from baseline at Day 10(N=189,190,201,204)	-12.0 (± 14.4)	-8.9 (± 14.9)	-11.4 (± 14.3)	-13.9 (± 16.0)

Change from baseline at Week 7(N=172,147,160,173)	-14.3 (± 16.8)	-12.5 (± 15.8)	-15.0 (± 16.0)	-17.0 (± 18.6)
Change from baseline at Week 13(N=161,135,150,160)	-15.2 (± 17.1)	-13.8 (± 16.0)	-14.6 (± 17.5)	-16.1 (± 18.0)
Change from baseline at Endpoint(N=215,215,220,218)	-11.9 (± 17.8)	-9.8 (± 17.2)	-12.2 (± 16.8)	-13.7 (± 18.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean of subjects reporting excellent/good with Patient global assessment

End point title	Change in mean of subjects reporting excellent/good with Patient global assessment
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End point description:

Patient Global Assessment responses were collected using a 5-point scale where 1 = excellent, 2 = good, 3 = fair, 4 = poor and 5 = unacceptable.

Full analysis set

End point type	Secondary
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End point timeframe:

At Day 10, Week 7 and Week 13

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Day 10 (N = 194, 194, 204, 207)	2.47 (± 0.98)	2.84 (± 0.97)	2.49 (± 0.92)	2.37 (± 0.95)
Week 7 (N = 176, 149, 161, 178)	2.42 (± 1.09)	2.57 (± 0.99)	2.39 (± 1.00)	2.30 (± 0.94)
Week 13 (N = 161, 136, 153, 160)	2.40 (± 1.08)	2.61 (± 1.19)	2.39 (± 1.08)	2.24 (± 1.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean Quality of Life Short Form 36

End point title	Change from baseline in mean Quality of Life Short Form 36
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End point description:

PF = Physical Functioning Score

CFB = Change from Baseline

PS = Physical Score

BPS = Bodily Pain Score

GHS = General Health Score

VS = Vitality Score

SFS = Social Functioning Score
ES = Emotional Score
MHS = Mental Health Score
CTOYA = Compare to one year ago

End point type	Secondary
End point timeframe:	
At Day 10, Week 7, Week 13 and LOCF	

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: units on scale				
arithmetic mean (standard deviation)				
PF - BASELINE - DAY 10 (N=192, 189, 199, 201)	49.3 (± 19.1)	49.3 (± 22.6)	48.2 (± 22.1)	50.4 (± 20.7)
PF - CFB - DAY 10 (N=192, 189, 199, 201)	5.1 (± 17.6)	3.9 (± 16.7)	4.9 (± 15.5)	5.2 (± 16.6)
PF - BASELINE - WEEK 7 (N=192, 189, 199, 201)	49.2 (± 18.7)	50.7 (± 22.8)	49.7 (± 21.6)	49.8 (± 21.1)
PF - CFB - WEEK 7 (N=192, 189, 199, 201)	7.6 (± 19.4)	4.5 (± 18.2)	8.2 (± 18.5)	7.9 (± 16.2)
PF - BASELINE - WEEK 13 (N=192, 189, 199, 201)	49.3 (± 18.7)	50.3 (± 22.9)	49.6 (± 21.6)	51.0 (± 21.1)
PF - CFB - WEEK 13 (N=192, 189, 199, 201)	7.2 (± 18.7)	3.8 (± 16.8)	6.3 (± 19.0)	6.6 (± 17.2)
PF - BASELINE - ENDPOINT(LOCF) (N=192,189,199,201)	49.0 (± 19.5)	48.4 (± 22.8)	48.1 (± 22.0)	49.8 (± 20.9)
PF - CFB - ENDPOINT (LOCF) (N=192, 189, 199, 201)	5.1 (± 19.9)	3.8 (± 18.9)	5.2 (± 17.9)	5.3 (± 16.9)
ROLE - PS - BASELINE - DAY 10 (N=192,186,199,199)	64.2 (± 23.8)	61.4 (± 27.1)	58.5 (± 26.1)	63.3 (± 26.3)
ROLE - PS - CFB - DAY 10 (N=192, 186, 199, 199)	5.6 (± 20.1)	5.4 (± 19.6)	5.0 (± 18.6)	6.0 (± 21.0)
ROLE - PS - BASELINE - WEEK 7 (N=173,147,158,171)	64.8 (± 24.3)	62.7 (± 26.4)	60.6 (± 24.5)	62.4 (± 26.7)
ROLE - PS - CFB - WEEK 7 (N=173, 147, 158, 171)	5.5 (± 22.9)	2.2 (± 21.2)	10.0 (± 21.1)	7.6 (± 22.9)
ROLE - PS - BASELINE - WEEK 13 (N=160,133,149,157)	64.6 (± 24.0)	61.8 (± 27.5)	61.0 (± 24.9)	63.4 (± 26.8)
ROLE - PS - CFB - WEEK 13 (N=160, 133, 149, 157)	5.8 (± 24.9)	4.1 (± 23.8)	5.9 (± 24.3)	5.0 (± 23.2)
ROLE-PS-BASELINE-ENDPOINT(LOCF)(N=215,215,216,214)	64.1 (± 24.4)	60.7 (± 26.8)	59.1 (± 26.1)	62.1 (± 26.6)
ROLE - PS - CFB - ENDPOINT(LOCF)(N=215,215,216,214)	3.8 (± 24.9)	1.5 (± 23.0)	4.6 (± 24.2)	3.9 (± 24.1)
BPS - BASELINE - DAY 10 (N=192, 194, 203, 207)	46.7 (± 14.9)	45.9 (± 18.4)	45.8 (± 16.9)	47.2 (± 17.5)
BPS - CFB - DAY 10 (N=192, 194, 203, 207)	10.3 (± 18.1)	7.8 (± 18.6)	8.4 (± 18.0)	11.4 (± 17.9)
BPS - BASELINE - WEEK 7 (N=173, 148, 160, 174)	47.5 (± 14.7)	47.1 (± 18.3)	46.9 (± 16.6)	46.7 (± 17.6)
BPS - CFB - WEEK 7 (N=173, 148, 160, 174)	10.3 (± 19.6)	11.0 (± 20.9)	12.1 (± 19.3)	12.7 (± 21.5)

BPS - BASELINE - WEEK 13 (N=161, 136, 152, 158)	47.4 (± 14.9)	46.8 (± 19.0)	46.8 (± 16.1)	47.2 (± 18.1)
BPS - CFB - WEEK 13 (N=161, 136, 152, 158)	13.4 (± 21.8)	11.0 (± 20.5)	12.9 (± 21.8)	12.2 (± 23.6)
BPS - BASELINE - ENDPOINT(LOCF)(N=214,218,219,217)	46.1 (± 15.3)	45.6 (± 18.4)	46.1 (± 17.9)	47.1 (± 17.2)
BPS - CFB - ENDPOINT(LOCF) (N=214, 218, 219, 217)	10.8 (± 21.6)	7.9 (± 21.5)	9.9 (± 21.6)	9.7 (± 22.1)
GHS - BASELINE - DAY 10 (N=189, 193, 199, 207)	64.7 (± 18.0)	63.3 (± 20.3)	60.6 (± 19.2)	63.6 (± 18.5)
GHS - CFB - DAY 10 (N=189, 193, 199, 207)	2.3 (± 11.0)	0.7 (± 11.2)	1.7 (± 11.0)	2.7 (± 11.6)
GHS - BASELINE - WEEK 7 (N=169, 147, 158, 174)	65.7 (± 17.6)	64.5 (± 20.2)	61.3 (± 18.1)	64.3 (± 17.9)
GHS - CFB - WEEK 7 (N=169, 147, 158, 174)	1.6 (± 13.5)	1.3 (± 12.0)	2.7 (± 11.4)	2.5 (± 14.0)
GHS - BASELINE - WEEK 13 (N=159, 132, 150, 158)	65.3 (± 17.7)	64.3 (± 21.0)	61.2 (± 18.3)	64.7 (± 18.1)
GHS - CFB - WEEK 13 (N=159, 132, 150, 158)	2.1 (± 12.8)	0.4 (± 13.4)	1.9 (± 12.6)	2.7 (± 13.6)
GHS - BASELINE - ENDPOINT(LOCF)(N=211,216,217,217)	64.6 (± 18.4)	62.5 (± 20.4)	61.7 (± 19.2)	63.7 (± 18.5)
GHS - CFB - ENDPOINT(LOCF) (N=211, 216, 217, 217)	1.3 (± 13.0)	0.0 (± 13.4)	1.0 (± 12.3)	1.6 (± 13.6)
VS - BASELINE - DAY 10 (N=187, 188, 197, 203)	52.3 (± 17.7)	53.6 (± 17.8)	49.5 (± 19.5)	54.8 (± 20.8)
VS - CFB - DAY 10 (N=187, 188, 197, 203)	5.2 (± 14.8)	2.6 (± 16.5)	3.3 (± 14.4)	4.8 (± 14.1)
VS - BASELINE - WEEK 7 (N=169, 146, 158, 172)	52.7 (± 18.1)	54.5 (± 18.2)	50.2 (± 19.0)	54.7 (± 20.2)
VS - CFB - WEEK 7 (N=169, 146, 158, 172)	3.3 (± 16.5)	2.6 (± 15.3)	5.0 (± 16.2)	3.4 (± 17.3)
VS - BASELINE - WEEK 13 (N=158, 131, 147, 156)	52.8 (± 18.6)	53.6 (± 18.6)	50.1 (± 19.3)	55.0 (± 20.4)
VS - CFB - WEEK 13 (N=158, 131, 147, 156)	4.4 (± 16.3)	1.9 (± 16.3)	4.8 (± 18.3)	5.1 (± 16.2)
VS - BASELINE - ENDPOINT(LOCF) (N=211,213,215,215)	52.5 (± 18.6)	53.3 (± 18.1)	50.4 (± 19.6)	54.4 (± 20.5)
VS - CFB - ENDPOINT(LOCF) (N=211, 213, 215, 215)	2.6 (± 16.1)	-0.6 (± 17.7)	3.0 (± 17.5)	2.6 (± 17.0)
SFS - BASELINE - DAY 10 (N=192, 194, 203, 207)	80.9 (± 20.4)	78.4 (± 24.2)	74.9 (± 24.7)	79.6 (± 23.2)
SFS - CFB - DAY 10 (N=192, 194, 203, 207)	2.5 (± 22.9)	2.6 (± 20.5)	1.6 (± 20.1)	2.5 (± 20.1)
SFS - BASELINE - WEEK 7 (N=173, 148, 160, 174)	81.1 (± 20.4)	80.3 (± 23.5)	76.6 (± 23.8)	80.4 (± 22.7)
SFS - CFB - WEEK 7 (N=173, 148, 160, 174)	4.4 (± 22.3)	-0.2 (± 23.2)	2.5 (± 20.9)	2.0 (± 25.0)
SFS - BASELINE - WEEK 13 (N=161, 136, 152, 158)	81.2 (± 20.4)	80.1 (± 24.0)	76.7 (± 23.7)	81.7 (± 22.1)
SFS - CFB - WEEK 13 (N=161, 136, 152, 158)	3.4 (± 23.1)	-2.1 (± 25.4)	2.6 (± 23.4)	0.2 (± 22.4)
SFS - BASELINE - ENDPOINT(LOCF)(N=214,218,219,217)	79.8 (± 21.2)	77.3 (± 24.7)	75.3 (± 24.8)	79.7 (± 23.0)
SFS - CFB - ENDPOINT(LOCF) (N=214, 218, 219, 217)	1.6 (± 24.3)	-3.8 (± 25.6)	1.4 (± 24.9)	-0.1 (± 24.1)
ES - BASELINE - DAY 10 (N=189, 193, 202, 205)	78.8 (± 24.6)	73.9 (± 28.4)	75.6 (± 26.3)	77.8 (± 27.3)
ES - CFB - DAY 10 (N=189, 193, 202, 205)	4.4 (± 20.3)	4.0 (± 22.7)	0.3 (± 20.9)	2.4 (± 18.7)
ES - BASELINE - WEEK 7 (N=170, 148, 157, 174)	79.0 (± 24.8)	75.0 (± 27.8)	77.2 (± 24.9)	78.1 (± 27.9)

ES - CFB - WEEK 7 (N=170, 148, 157, 174)	2.9 (± 24.1)	2.2 (± 21.8)	2.8 (± 25.3)	2.6 (± 23.5)
ES - BASELINE - WEEK 13 (N=160, 136, 150, 158)	78.5 (± 24.3)	75.1 (± 28.2)	77.1 (± 24.9)	78.6 (± 28.0)
ES - CFB - WEEK 13 (N=160, 136, 150, 158)	3.4 (± 25.3)	0.7 (± 25.8)	1.4 (± 22.0)	0.3 (± 27.1)
ES - BASELINE - ENDPOINT(LOCF) (N=213,218,218,217)	78.4 (± 24.8)	73.2 (± 28.8)	75.4 (± 26.6)	77.4 (± 27.1)
ES - CFB - ENDPOINT(LOCF) (N=213, 218, 218, 217)	1.2 (± 25.5)	-1.9 (± 26.3)	-0.1 (± 23.3)	-1.0 (± 26.3)
MHS - BASELINE - DAY 10 (N=187, 188, 197, 202)	75.9 (± 14.7)	74.4 (± 19.2)	72.9 (± 17.7)	75.7 (± 18.7)
MHS - CFB - DAY 10 (N=187, 188, 197, 202)	4.4 (± 12.8)	0.5 (± 13.8)	1.5 (± 15.1)	2.5 (± 14.5)
MHS - BASELINE - WEEK 7 (N=169, 146, 158, 172)	76.4 (± 14.5)	76.2 (± 18.5)	73.0 (± 17.5)	76.0 (± 18.5)
MHS - CFB - WEEK 7 (N=169, 146, 158, 172)	2.3 (± 14.8)	-0.3 (± 15.1)	1.7 (± 16.1)	1.4 (± 15.5)
MHS - BASELINE - WEEK 13 (N=158, 131, 147, 156)	76.4 (± 14.2)	76.3 (± 18.6)	72.8 (± 17.8)	76.7 (± 18.6)
MHS - CFB - WEEK 13 (N=158, 131, 147, 156)	1.4 (± 15.6)	-1.4 (± 15.0)	2.1 (± 17.3)	1.7 (± 16.8)
MHS - BASELINE - ENDPOINT(LOCF)(N=211,213,215,214)	75.8 (± 14.9)	73.8 (± 19.2)	73.5 (± 18.0)	75.6 (± 18.5)
MHS - CFB - ENDPOINT(LOCF) (N=211, 213, 215, 214)	0.9 (± 15.7)	-2.2 (± 16.3)	0.1 (± 16.6)	0.4 (± 18.0)
CTOYA - BASELINE - DAY 10 (N=192, 195, 203, 207)	3.02 (± 0.43)	2.97 (± 0.45)	3.01 (± 0.53)	3.00 (± 0.39)
CTOYA - CFB - DAY 10 (N=192, 195, 203, 207)	-0.30 (± 0.76)	-0.12 (± 0.76)	-0.23 (± 0.79)	-0.26 (± 0.78)
CTOYA - BASELINE - WEEK 7 (N=176, 148, 160, 175)	3.03 (± 0.41)	2.96 (± 0.42)	3.03 (± 0.51)	3.00 (± 0.39)
CTOYA - CFB - WEEK 7 (N=176, 148, 160, 175)	0.01 (± 0.62)	-0.09 (± 0.71)	-0.16 (± 0.80)	-0.11 (± 0.66)
CTOYA - BASELINE - WEEK 13 (N=162, 136, 152, 160)	3.02 (± 0.42)	2.99 (± 0.44)	3.02 (± 0.52)	3.00 (± 0.37)
CTOYA - CFB - WEEK 13 (N=162, 136, 152, 160)	-0.17 (± 0.72)	-0.10 (± 0.62)	-0.09 (± 0.73)	-0.05 (± 0.65)
CTOYA-BASELINE - ENDPOINT(LOCF)(N=216,218,219,217)	3.02 (± 0.45)	2.98 (± 0.48)	3.01 (± 0.53)	3.01 (± 0.41)
CTOYA - CFB - ENDPOINT(LOCF) (N=216,218,219,217)	-0.12 (± 0.73)	-0.01 (± 0.75)	-0.09 (± 0.74)	-0.04 (± 0.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean Quality of Life Patient Generated Index

End point title	Change from baseline in mean Quality of Life Patient Generated Index
End point description:	
Full analysis set	
End point type	Secondary
End point timeframe:	
At Day 10, Week 7, Week 13 and Endpoint (LOCF)	

End point values	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg	Test: Ibu 400mg + Para 1000mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	224	222	222	224
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline (N = 224, 222, 222, 224)	2.55 (± 1.17)	2.42 (± 1.23)	2.50 (± 1.13)	2.41 (± 1.21)
Change from baseline at Day 10(N=186,190,190,194)	0.51 (± 1.33)	0.39 (± 1.25)	0.42 (± 1.22)	0.74 (± 1.43)
Change from baseline at Week 7(N=170,143,151,166)	0.58 (± 1.46)	0.72 (± 1.37)	0.76 (± 1.43)	0.91 (± 1.41)
Change from baseline at Week 13(N=156,132,140,151)	0.76 (± 1.42)	0.56 (± 1.21)	0.76 (± 1.32)	0.96 (± 1.46)
Change from baseline at Endpoint(N=210,212,210,212)	0.60 (± 1.41)	0.44 (± 1.20)	0.69 (± 1.36)	0.76 (± 1.46)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 13

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Reference: Ibu 400mg
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Reporting group description: -

Reporting group title	Reference: Para 1000mg
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Reporting group description: -

Reporting group title	Test: Ibu 200mg + Para 500mg
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Reporting group description: -

Reporting group title	Test: Ibu 400mg + Para 1000mg
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Reporting group description: -

Serious adverse events	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 224 (1.34%)	2 / 222 (0.90%)	0 / 222 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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

Vascular disorders			
Ruptured abdominal aortic aneurism			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Blood and lymphatic system disorders			
Macrocytosis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Neutropenia			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Pulmonary embolism			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 222 (0.00%)	0 / 222 (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
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Test: Ibu 400mg + Para 1000mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 224 (4.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 224 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ruptured abdominal aortic aneurism			
subjects affected / exposed	0 / 224 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 224 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 224 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Macrocytosis			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye haemorrhage			

subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 224 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 224 (0.00%)		
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	Reference: Ibu 400mg	Reference: Para 1000mg	Test: Ibu 200mg + Para 500mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 224 (100.00%)	222 / 222 (100.00%)	222 / 222 (100.00%)
Investigations			
Blood urea increased			
subjects affected / exposed	12 / 224 (5.36%)	8 / 222 (3.60%)	13 / 222 (5.86%)
occurrences (all)	12	8	13
Gamma Glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 224 (0.89%) 2	18 / 222 (8.11%) 18	14 / 222 (6.31%) 14
Liver function test abnormal subjects affected / exposed occurrences (all)	1 / 224 (0.45%) 1	14 / 222 (6.31%) 14	6 / 222 (2.70%) 6
Nervous system disorders Headache subjects affected / exposed occurrences (all)	17 / 224 (7.59%) 26	25 / 222 (11.26%) 37	26 / 222 (11.71%) 40
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 224 (1.34%) 3	2 / 222 (0.90%) 2	2 / 222 (0.90%) 2
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	5 / 224 (2.23%) 5	2 / 222 (0.90%) 2	6 / 222 (2.70%) 6
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	12 / 224 (5.36%) 13	5 / 222 (2.25%) 6	7 / 222 (3.15%) 7
Diarrhoea subjects affected / exposed occurrences (all)	19 / 224 (8.48%) 23	22 / 222 (9.91%) 28	16 / 222 (7.21%) 20
Dyspepsia subjects affected / exposed occurrences (all)	23 / 224 (10.27%) 31	14 / 222 (6.31%) 17	38 / 222 (17.12%) 48
Nausea subjects affected / exposed occurrences (all)	16 / 224 (7.14%) 17	13 / 222 (5.86%) 14	20 / 222 (9.01%) 25
Abdominal distension subjects affected / exposed occurrences (all)	5 / 224 (2.23%) 5	2 / 222 (0.90%) 2	5 / 222 (2.25%) 6
Abdominal pain subjects affected / exposed occurrences (all)	2 / 224 (0.89%) 2	5 / 222 (2.25%) 5	2 / 222 (0.90%) 2

Abdominal pain upper subjects affected / exposed occurrences (all)	9 / 224 (4.02%) 14	8 / 222 (3.60%) 13	7 / 222 (3.15%) 9
Flatulence subjects affected / exposed occurrences (all)	5 / 224 (2.23%) 5	4 / 222 (1.80%) 4	4 / 222 (1.80%) 4
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	6 / 224 (2.68%) 7	3 / 222 (1.35%) 5	3 / 222 (1.35%) 3
Stomach discomfort subjects affected / exposed occurrences (all)	10 / 224 (4.46%) 12	5 / 222 (2.25%) 5	9 / 222 (4.05%) 12
Vomiting subjects affected / exposed occurrences (all)	7 / 224 (3.13%) 7	3 / 222 (1.35%) 3	9 / 222 (4.05%) 10
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	7 / 224 (3.13%) 8	9 / 222 (4.05%) 9	4 / 222 (1.80%) 4
Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	12 / 224 (5.36%) 12	5 / 222 (2.25%) 5	5 / 222 (2.25%) 6
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	30 / 224 (13.39%) 36	38 / 222 (17.12%) 63	38 / 222 (17.12%) 56
Back pain subjects affected / exposed occurrences (all)	11 / 224 (4.91%) 19	11 / 222 (4.95%) 17	17 / 222 (7.66%) 17
Pain in extremity subjects affected / exposed occurrences (all)	10 / 224 (4.46%) 15	19 / 222 (8.56%) 22	17 / 222 (7.66%) 19
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 224 (4.91%) 13	22 / 222 (9.91%) 30	20 / 222 (9.01%) 23

Non-serious adverse events	Test: Ibu 400mg + Para 1000mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 224 (100.00%)		
Investigations			
Blood urea increased			
subjects affected / exposed	11 / 224 (4.91%)		
occurrences (all)	11		
Gamma Glutamyltransferase increased			
subjects affected / exposed	10 / 224 (4.46%)		
occurrences (all)	10		
Liver function test abnormal			
subjects affected / exposed	8 / 224 (3.57%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 224 (12.05%)		
occurrences (all)	42		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 224 (2.23%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 224 (1.79%)		
occurrences (all)	4		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 224 (3.57%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	28 / 224 (12.50%)		
occurrences (all)	32		
Dyspepsia			
subjects affected / exposed	27 / 224 (12.05%)		
occurrences (all)	49		

Nausea			
subjects affected / exposed	15 / 224 (6.70%)		
occurrences (all)	17		
Abdominal distension			
subjects affected / exposed	4 / 224 (1.79%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	0 / 224 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	11 / 224 (4.91%)		
occurrences (all)	14		
Flatulence			
subjects affected / exposed	5 / 224 (2.23%)		
occurrences (all)	5		
Gastroesophageal reflux disease			
subjects affected / exposed	5 / 224 (2.23%)		
occurrences (all)	5		
Stomach discomfort			
subjects affected / exposed	8 / 224 (3.57%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	9 / 224 (4.02%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 224 (5.80%)		
occurrences (all)	14		
Pharyngolaryngeal pain			
subjects affected / exposed	7 / 224 (3.13%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 224 (13.39%)		
occurrences (all)	37		
Back pain			

subjects affected / exposed occurrences (all)	12 / 224 (5.36%) 17		
Pain in extremity subjects affected / exposed occurrences (all)	12 / 224 (5.36%) 17		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 224 (8.93%) 22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2007	Amendment 01 added an exclusion criterion of ankle oedema, to assist in the exclusion of potential participants who may have had cardiovascular disease. Additionally, this amendment dispensed with the original protocol requirement for a general physical examination to be conducted prior to entry. As potential participants were to have a musculoskeletal examination by a study metrologist, it was felt that additional examination was unnecessary, also added stratification of patients to treatment depending on a classification of OA or non-OA according to an initial X-ray review. This was to ensure an even distribution of OA and non-OA patients across the groups without waiting for a detailed review, and documented a change of analytical laboratory conducting the haematology, biochemistry and urinalysis. This was required because the original laboratory was unable to supply evidence of GLP accreditation. No patients were enrolled in the study until after amendment 01 had been approved.
13 March 2007	Amendment 02 changed the primary safety endpoint to the incidence of moderate and severe AEs regardless of the relationship to assigned treatment, as opposed to those classed as being possibly, probably or definitely related to treatment, also clarified the inclusion criterion relating to frequency of knee pain experienced by potential participants, to state that they must have experienced pain on at least four of seven days preceding the screening visit, added to the exclusion criteria any past history of GI bleeding. It also excluded patients taking methotrexate (at the request of Nottinghamshire Primary Care Trust), patients taking warfarin and other anticoagulants (at the request of the FDA), with the exception of those taking low dose aspirin who had been stable for 30 days prior to taking the 1st dose of study medication, added additional urinary pregnancy tests for female subjects, to be conducted at the Week 7, Week 13 assessments. Initially it was intended that patient medication packs would be dispensed on each of the Baseline, Day 10 and Week 7 visits. However, it was decided that patients would be issued with all their study medication at the baseline visit, and this was documented, changed the planned analysis definition of full analysis dataset, from those who took at least one dose of study medication, had at least one post-baseline assessment, to those who took at least one dose of study medication, regardless of whether a post-baseline assessment was available. The original protocol specified that high and low dose combinations would be compared to paracetamol alone, revised the statistical section to state that the combinations would also be compared to ibuprofen alone. It further made provision for the use of additional supportive analyses using baseline observation carried forward as one of the strategies for dealing with missing data. These change was requested by the FDA. No patients were enrolled into the study before amendment 02 was approved.

15 August 2007	Amendment 03 added to the recruitment methods used for the study. Originally, patients were to be enrolled through General Practices in Nottinghamshire. This amendment allowed for additional recruitment through advertisements in local newspapers, magazines, posters and on local radio. It also allowed for recruitment through General Practices in the additional counties of Derbyshire, Staffordshire and Leicestershire. These changes were initiated by the Sponsor as recruitment was falling behind target and it was felt necessary to increase the population from which recruitment was made. It was later decided that it was not necessary to use General Practices in Derbyshire, Staffordshire and Leicestershire and hence Primary Care Trust approval in these counties was not sought, also changed the inclusion criterion requiring patients to experience knee pain of between 30 and 80mm on a VAS whilst walking on a flat surface, to cover the same level of pain but which occurred during any 1 or more of walking on a flat surface, or going up and down stairs, or at night while in bed, or while sitting or lying or while standing upright. This change was initiated by both the Investigator and the Sponsor as it was deemed that a positive response in any of these circumstances was indicative of knee pain and would enhance both the recruitment potential and the applicability of the data to the general population. This Amendment implemented when 233 patients had been randomised to the study.
10 September 2007	Amendment 04 added seven Synexus sites to the study, in order to aid recruitment. It allowed for patients recruited by Synexus to have their assessment visits take place at the sites, with no home visits being made for these patients. This change was initiated by the Sponsor to address recruitment difficulties. Amendment 04 was implemented when 548 patients had been screened and 408 had been randomised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported