Clinical trial results:
A Phase III, Two-Part, Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial to Assess the Relative Efficacy and Tolerability of Two Doses of MK-0663/Etoricoxib in Patients with Rheumatoid Arthritis (MK-0663-107)

Summary

EudraCT number	2010-019871-31
Trial protocol	FI BE AT LT GB DE SK CZ
Global end of trial date	29 July 2014

Results information

Result version number	v2 (current)
This version publication date	19 March 2016
First version publication date	03 June 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	0663-107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01208181
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: MK-0663-107

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	29 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a 2-part (6 weeks duration for each part), randomized, double-blind, placebo-controlled study in participants with rheumatoid arthritis. The hypothesis is that etoricoxib (60 mg and 90 mg) administration will demonstrate superior efficacy compared to placebo after 6 weeks of treatment, as measured by the greater mean improvement from baseline in the Disease Activity Score C-Reactive Protein (DAS-28 CRP), and by the greater mean improvement in Patient Global Assessment of Pain (PGAP) from baseline over 6 weeks of treatment. Additionally, the added benefit of increasing the dose of etoricoxib from 60 mg to 90 mg will be assessed in the second part of the study.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2010
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: 216
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Peru: 39
Country: Number of subjects enrolled	Romania: 127
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	South Africa: 69
Country: Number of subjects enrolled	Taiwan: 74
Country: Number of subjects enrolled	United States: 309
Country: Number of subjects enrolled	Argentina: 154
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Colombia: 49

Country: Number of subjects enrolled	Guatemala: 51
Country: Number of subjects enrolled	India: 83
Country: Number of subjects enrolled	Mexico: 57
Worldwide total number of subjects	1404
EEA total number of subjects	455

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)	1148
From 65 to 84 years	256
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 164 sites enrolled participants in this study.

Pre-assignment

Screening details:

A total of 1765 patients were screened for inclusion in the study and 1404 of these patients were randomized. Of the 361 patients who were not randomized; 295 of these patients were excluded due to screen failures and 66 of these patients were not randomized due to other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Placebo

Arm description:

The placebo treatment group will receive placebo to etoricoxib tablets administered orally once daily for 6 weeks in Part 1 of the study.

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

Dosage and administration details:

The placebo treatment group will receive placebo to etoricoxib tablets administered orally once daily for 6 weeks in Part 1 of the study.

Arm title	Part 1: Etoricoxib 60 mg

Arm description:

The etoricoxib 60 mg treatment group will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.

Arm type	Experimental
Investigational medicinal product name	Etoricoxib 60 mg
Investigational medicinal product code	
Other name	MK-0663
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The etoricoxib 60 mg treatment group will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.

Arm title	Part 1: Etoricoxib 90 mg

Arm description:

The etoricoxib 90 mg treatment sequence will receive etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.

Arm type	Experimental

Investigational medicinal product name	Etoricoxib 90 mg
Investigational medicinal product code	
Other name	MK-0663
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The etoricoxib 90 mg treatment sequence will receive etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.

Number of subjects in period 1	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg
Started	118	818	468
Completed	96	719	413
Not completed	22	99	55
Consent withdrawn by subject	-	11	10
Physician decision	-	4	-
Technical problem	-	5	-
Adverse event, non-fatal	4	26	24
Non-compliance with study drug	-	1	1
Lost to follow-up	1	5	3
Lack of efficacy	17	37	12
Protocol deviation	-	10	5

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg

Arm description:

The Etoricoxib 60 mg/etoricoxib 60 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 and Part 2 of the study

Arm type	Experimental
Investigational medicinal product name	Etoricoxib 60 mg/etoricoxib 60 mg
Investigational medicinal product code	
Other name	MK-0663
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The Etoricoxib 60 mg/etoricoxib 60 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 and Part 2 of the study.

Arm title	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg

Arm description:

The etoricoxib 60 mg/etoricoxib 90 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study and etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 2 of the study.

Arm type	Experimental
Investigational medicinal product name	Etoricoxib 60 mg/etoricoxib 90 mg
Investigational medicinal product code	
Other name	MK-0663
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The etoricoxib 60 mg/etoricoxib 90 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study and etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 2 of the study.

Number of subjects in period 2[1]	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg
Started	350	363
Completed	334	343
Not completed	16	20
Physician decision	1	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	6	7
Non-compliance with study drug	1	1
Lost to follow-up	1	2
Lack of efficacy	5	7
Protocol deviation	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who received etoricoxib 60 mg and completed Part I of the trial continued into Part II and received either etoricoxib 60 mg or etoricoxib 90 mg. Therefore, the number of participants completing Part I for each study arm is not consistent with the number of participants starting Part II for each study arm.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Placebo
Reporting group description:	
The placebo treatment group will receive placebo to etoricoxib tablets administered orally once daily for 6 weeks in Part 1 of the study.	
Reporting group title	Part 1: Etoricoxib 60 mg
Reporting group description:	
The etoricoxib 60 mg treatment group will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.	
Reporting group title	Part 1: Etoricoxib 90 mg
Reporting group description:	
The etoricoxib 90 mg treatment sequence will receive etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.	

Reporting group values	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg
Number of subjects	118	818	468
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)	102	671	375
From 65-84 years	16	147	93
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.6	53.8	54
standard deviation	± 11	± 11.9	± 12.3
Gender categorical Units: Subjects			
Female	100	677	395
Male	18	141	73
Disease Activity Score using C reactive protein (DAS28-CRP)			
The DAS28-CRP index (0 - 10 Range) is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity, and C-reactive protein (CRP). For each observation (Baseline, Week 2, 4, 6, 10, 12), components were combined into a single DAS28-CRP score using the following algorithm: 0.56*square root (sqrt) (tender joint count [28])+0.28*sqrt(swollen joint count [28])+0.36* ln(crp+1) + 0.014* Patient Global Assessment of Disease Activity + 0.96. (N = 732, 426, 103 for Etoricoxib 60 mg and 90 mg, and Placebo)			
Units: Scores on a scale			
arithmetic mean	5.65	5.64	5.62
standard deviation	± 1.12	± 0.99	± 1
Patient Global Assessment of Pain			

A participant overall assessment of pain on a visual analog scale (VAS) were assessed with a question concerning the amount of pain due to arthritis during the past 48 hours. Pain was assessed on an 100 mm VAS scale with a left-hand marker "no pain" (0 mm) or right-hand marker "extreme pain" (100 mm). (N = 751, 430, 108 for Etoricoxib 60 mg, Etoricoxib 90 mg, and Placebo)			
Units: Scores on a scale			
arithmetic mean	74.08	70.84	70.58
standard deviation	± 14.23	± 15.5	± 15.02

Reporting group values	Total		
Number of subjects	1404		
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)	1148		
From 65-84 years	256		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1172		
Male	232		
Disease Activity Score using C reactive protein (DAS28-CRP)			
The DAS28-CRP index (0 - 10 Range) is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity, and C-reactive protein (CRP). For each observation (Baseline, Week 2, 4, 6, 10, 12), components were combined into a single DAS28-CRP score using the following algorithm: 0.56*square root (sqrt) (tender joint count [28])+0.28*sqrt(swollen joint count [28])+0.36* ln(crp+1) + 0.014* Patient Global Assessment of Disease Activity + 0.96. (N = 732, 426, 103 for Etoricoxib 60 mg and 90 mg, and Placebo)			
Units: Scores on a scale			
arithmetic mean			
standard deviation	-		
Patient Global Assessment of Pain			
A participant overall assessment of pain on a visual analog scale (VAS) were assessed with a question concerning the amount of pain due to arthritis during the past 48 hours. Pain was assessed on an 100 mm VAS scale with a left-hand marker "no pain" (0 mm) or right-hand marker "extreme pain" (100 mm). (N = 751, 430, 108 for Etoricoxib 60 mg, Etoricoxib 90 mg, and Placebo)			
Units: Scores on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Part 1: Placebo
Reporting group description:	
The placebo treatment group will receive placebo to etoricoxib tablets administered orally once daily for 6 weeks in Part 1 of the study.	
Reporting group title	Part 1: Etoricoxib 60 mg
Reporting group description:	
The etoricoxib 60 mg treatment group will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.	
Reporting group title	Part 1: Etoricoxib 90 mg
Reporting group description:	
The etoricoxib 90 mg treatment sequence will receive etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.	
Reporting group title	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg
Reporting group description:	
The Etoricoxib 60 mg/etoricoxib 60 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 and Part 2 of the study	
Reporting group title	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg
Reporting group description:	
The etoricoxib 60 mg/etoricoxib 90 mg treatment sequence will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study and etoricoxib 90 mg tablets administered orally once daily for 6 weeks in Part 2 of the study.	
Subject analysis set title	Part 1: Etoricoxib 60 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
The etoricoxib 60 mg treatment group will receive etoricoxib 60 mg tablets administered orally once daily for 6 weeks in Part 1 of the study.	

Primary: Time-Weighted Average Change From Baseline in Disease Activity Score Using C-Reactive Protein [DAS28-CRP] in Part 1 (Etoricoxib vs. Placebo)

End point title	Time-Weighted Average Change From Baseline in Disease Activity Score Using C-Reactive Protein [DAS28-CRP] in Part 1 (Etoricoxib vs. Placebo)
End point description:	
The DAS28-CRP index (0-10 Range) is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity, and C-reactive protein (CRP). For each observation (Baseline, Week 2, 4, 6, 10, 12), components were combined into a single DAS28-CRP score using the following algorithm: 0.56*square root (sqrt) (tender joint count [28])+0.28*sqrt(swollen joint count [28])+0.36* ln(crp+1) + 0.014* Patient Global Assessment of Disease Activity + 0.96. The primary objectives of the study compared the efficacy of etoricoxib (90 mg, 60 mg) to placebo in Part 1 of this study so data for only these 3 arms are displayed. The modified intention-to-treat (mITT) population in Part 1 consisted of all randomized participants receiving at least 1 dose of study medication, had baseline data for the analysis endpoint, and least one post-randomization measurement for that endpoint.	
End point type	Primary
End point timeframe:	
Baseline and Week 6	

End point values	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	732	426	
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-1.1 (-1.29 to -0.9)	-1.39 (-1.48 to -1.3)	-1.37 (-1.48 to -1.26)	

Statistical analyses

Statistical analysis title	Treatment Difference (Etoricoxib 60 mg v. Placebo)

Statistical analysis description:

Difference in the least squares means between change from baseline in DAS28-CRP for participants taking Etoricoxib 60 mg at Week 6 vs. change from baseline in DAS28-CRP for participants taking Placebo at Week 6.

Comparison groups	Part 1: Etoricoxib 60 mg v Part 1: Placebo
Number of subjects included in analysis	835
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Tukey-Ciminera-Heysetrend test
Parameter estimate	Difference in least squares mean
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.09

Statistical analysis title	Treatment Difference (Etoricoxib 90 mg v. Placebo)

Statistical analysis description:

Difference in the least squares means between change from baseline in DAS28-CRP for participants taking Etoricoxib 90 mg at Week 6 vs. change from baseline in DAS28-CRP for participants taking Placebo at Week 6

Comparison groups	Part 1: Placebo v Part 1: Etoricoxib 90 mg
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Tukey-Ciminera-Heysetrend test
Parameter estimate	Difference in least squares mean
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.06

Primary: Time-Weighted Average Change From Baseline in Patient Global Assessment of Pain in Part 1 (Etoricoxib vs. Placebo)

End point title	Time-Weighted Average Change From Baseline in Patient Global Assessment of Pain in Part 1 (Etoricoxib vs. Placebo)

End point description:

A participant overall assessment of pain on a visual analog scale (VAS) was assessed with a question concerning the amount of pain due to arthritis during the past 48 hours. Pain was assessed on an 100 mm VAS scale with a left-hand marker "no pain" (0 mm) or right-hand marker "extreme pain" (100 mm). The primary objectives of the study compared the efficacy of etoricoxib (90 mg, 60 mg) to placebo in Part 1 of this study so data for only these 3 arms are displayed. The mITT population in Part 1 consisted of all randomized participants receiving at least 1 dose of study medication, had baseline data for the analysis endpoint, and least one post-randomization measurement for that endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 6

End point values	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	751	430	
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-20.26 (-24.04 to -16.48)	-28.25 (-30.05 to -26.44)	-30.96 (-33.13 to -28.79)	

Statistical analyses

Statistical analysis title	Treatment Difference (Etoricoxib 60 mg v. Placebo)

Statistical analysis description:

Change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Etoricoxib 60 mg minus change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Placebo.

Comparison groups	Part 1: Etoricoxib 60 mg v Part 1: Placebo
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Tukey-Ciminera-Heyse trend test
Parameter estimate	Difference in the least squares mean
Point estimate	-7.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.85
upper limit	-4.13

Statistical analysis title	Treatment Difference (Etoricoxib 90 mg v. Placebo)

Statistical analysis description:

Change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Etoricoxib 90 mg minus change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Placebo.

Comparison groups	Part 1: Placebo v Part 1: Etoricoxib 90 mg
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Tukey-Ciminera-Heyse trend test
Parameter estimate	Difference in least squares mean
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.74
upper limit	-6.66

Primary: Percentage of Participants Who Experienced at Least One Adverse Event (AE) in Part 1 and Part 2

End point title	Percentage of Participants Who Experienced at Least One Adverse Event (AE) in Part 1 and Part 2[1][2]

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure. All Subjects as Treated (ASaT) population, defined as all randomized participants who received at least one study drug. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population.

End point type	Primary

End point timeframe:

Up to Week 16

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis of this end point was specified in the protocol or the statistical analysis plan.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis of this end point was specified in the protocol or the statistical analysis plan.

End point values	Part 1: Placebo	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg	Part 1: Etoricoxib 90 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	350	363	467
Units: Percentage of Participants				

number (not applicable)	25.4	19.1	24.5	36

End point values	Part 1: Etoricoxib 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	819			
Units: Percentage of Participants				
number (not applicable)	30.3			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Discontinued Study Drug Due to an AE in Part 1 and Part 2

End point title	Percentage of Participants Who Discontinued Study Drug Due to an AE in Part 1 and Part 2[3][4]

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure. ASaT population defined as all randomized participants who received at least one study drug. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population.

End point type	Primary

End point timeframe:

Up to Week 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis of this end point was specified in the protocol or the statistical analysis plan.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis of this end point was specified in the protocol or the statistical analysis plan.

End point values	Part 1: Placebo	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg	Part 1: Etoricoxib 90 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	350	363	467
Units: Percentage of Participants				
number (not applicable)	3.4	1.4	1.9	5.1

End point values	Part 1: Etoricoxib 60 mg			

Subject group type	Subject analysis set			
Number of subjects analysed	819			
Units: Percentage of Participants				
number (not applicable)	3.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-Weighted Average Change From Baseline in DAS28-CRP in Part 1 (Etoricoxib 90 mg vs. Etoricoxib 60 mg)

End point title	Time-Weighted Average Change From Baseline in DAS28-CRP in Part 1 (Etoricoxib 90 mg vs. Etoricoxib 60 mg)

End point description:

The DAS28-CRP index (0 - 10 range) is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity, and C-reactive protein (CRP). For each observation (Baseline, Week 2, 4, 6, 10, 12), components were combined into a single DAS28-CRP score using the following algorithm: 0.56*square root (sqrt) (tender joint count [28])+0.28*sqrt(swollen joint count [28])+0.36* ln(crp+1) + 0.014* Patient Global Assessment of Disease Activity + 0.96. A key secondary objective was to compare the relative efficacy between etoricoxib 90 mg and 60 mg in Part 1 of this study. The mITT population in Part 1 consisted of all randomized participants receiving at least 1 dose of study medication, had baseline data for the analysis endpoint, and least one post-randomization measurement for that endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	732	426	
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-1.1 (-1.29 to -0.9)	-1.39 (-1.48 to -1.3)	-1.37 (-1.48 to -1.26)	

Statistical analyses

Statistical analysis title	Treatment Difference (Etoricoxib 60 mg vs. 90 mg)

Statistical analysis description:

Difference in the least squares means between change from baseline in DAS28-CRP for participants taking Etoricoxib 60 mg at Week 6 vs. change from baseline in DAS28-CRP for participants taking Etoricoxib 90 mg at Week 6.

Comparison groups	Part 1: Etoricoxib 60 mg v Part 1: Etoricoxib 90 mg

Number of subjects included in analysis	1158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Tukey-Ciminera-Heysetrend test
Parameter estimate	Difference in least squares mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.14

Secondary: Time-Weighted Mean Change From Baseline in Patient Global Assessment of Pain in Part 1 (Etoricoxib 90 mg vs. Etoricoxib 60 mg)

End point title	Time-Weighted Mean Change From Baseline in Patient Global Assessment of Pain in Part 1 (Etoricoxib 90 mg vs. Etoricoxib 60 mg)

End point description:

A participant overall assessment of pain on a visual analog scale (VAS) was assessed with a question concerning the amount of pain due to arthritis during the past 48 hours. Pain was assessed on an 100 mm VAS scale with a left-hand marker "no pain" (0 mm) or right-hand marker "extreme pain" (100 mm). A key secondary objective was to compare the relative efficacy between etoricoxib 90 mg and 60 mg in Part 1 of this study. The mITT population in Part 1 consisted of all randomized participants receiving at least 1 dose of study medication, had baseline data for the analysis endpoint, and least one post-randomization measurement for that endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	751	430	
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-20.26 (-24.04 to -16.48)	-28.25 (-30.05 to -26.44)	-30.96 (-33.13 to -28.79)	

Statistical analyses

Statistical analysis title	Treatment Difference (Etoricoxib 60 mg vs. 90 mg)

Statistical analysis description:

Change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Etoricoxib 60 mg minus change from baseline in Patient Global Assessment of Disease Activity at Week 6 for participants treated with Etoricoxib 90 mg.

Comparison groups	Part 1: Etoricoxib 60 mg v Part 1: Etoricoxib 90 mg

Number of subjects included in analysis	1181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Tukey-Ciminera-Heyse trend test
Parameter estimate	Difference in least squares mean
Point estimate	-2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.98
upper limit	-0.45

Secondary: Average change from Week 6 in Patient Global Assessment of Pain Over Weeks 10 and 12 in Part 2 Among Pain Inadequate Responders from Part 1

End point title	Average change from Week 6 in Patient Global Assessment of Pain Over Weeks 10 and 12 in Part 2 Among Pain Inadequate Responders from Part 1

End point description:

A participant overall assessment of pain on a visual analog scale (VAS) was assessed with a question concerning the amount of pain due to arthritis during the past 48 hours assessed on an 100 mm VAS scale; left-hand "no pain" (0 mm) or right-hand "extreme pain" (100 mm). Inadequate responders to etoricoxib 60 mg in Part 1 (<50% improvement from baseline in PGAP [VAS] at Week 6) were evaluated for an incremental benefit of increasing the etoricoxib dose to 90 mg in Part 2 compared to remaining on 60 mg in Part 2 for average change from Week 6 over Weeks 10 and 12 in Patient Global Assessment of Pain score. Therefore, data for only these 2 arms are displayed. This population (a subpopulation of the mITT population) was composed of pain inadequate responder (PIRs) in Part 1. PIRs were defined as participants with <50% improvement from baseline in Patient Global Assessment of Pain (VAS) at Week 6 and received at least one dose of study medication in Part 2.

End point type	Secondary

End point timeframe:

Week 6 and Week 10 to Week 12

End point values	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg	Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	187		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-11.96 (-14.96 to -8.97)	-10.35 (-13.32 to -7.39)		

Statistical analyses

Statistical analysis title	Treatment Difference (Etoricoxib 60 mg vs. 90 mg)

Statistical analysis description:

Change from Week 6 in Patient Global Assessment of Disease Activity over Weeks 10 to 12 for participants treated with Etoricoxib 60 mg/Etoricoxib 60 mg minus change from Week 6 in Patient Global

Assessment of Disease Activity over Weeks 10 to 12 for participants treated with Etoricoxib 60 mg/Etoricoxib 90 mg.

Comparison groups	Part 1/2: Etoricoxib 60 mg/etoricoxib 60 mg v Part 1/2: Etoricoxib 60 mg/etoricoxib 90 mg
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327
Method	Covariance model
Parameter estimate	Difference in the least squares mean
Point estimate	1.61
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.49
upper limit	3.71

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 16

Adverse event reporting additional description:

The All Participants as Treated (APaT) population was used for the analysis of safety data in this study and consisted of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Part 1: Placebo

Reporting group description:

The placebo treatment group will receive placebo to etoricoxib tablets administered orally once daily in Part 1 of the study.

Reporting group title	Part 1: Etoricoxib 60 mg

Reporting group description:

The Etoricoxib 60 mg treatment group will receive etoricoxib tablets 60 mg administered orally once daily in Part 1 of the study.

Reporting group title	Part 1: Etoricoxib 90 mg

Reporting group description:

The Etoricoxib 90 mg treatment group will receive etoricoxib tablets 90 mg administered orally once daily in Part 1 of the study.

Reporting group title	Part 1/2: Etoricoxib 60 mg/60 mg

Reporting group description:

The Etoricoxib 60 mg/Etoricoxib 60 mg treatment sequence will receive etoricoxib tablets 60 mg administered orally once daily in Part 1 and Part 2 of the study.

Reporting group title	Part 1/2: Etoricoxib 60 mg/90 mg

Reporting group description:

The Etoricoxib 60 mg/Etoricoxib 90 mg treatment sequence will receive etoricoxib tablets 60 mg administered orally once daily in Part 1 of the study and etoricoxib tablets 90 mg administered orally once daily in Part 2 of the study.

Serious adverse events	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 118 (0.00%)	7 / 819 (0.85%)	2 / 467 (0.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			

subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Atrial fibrillation			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Coronary artery disease			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 118 (0.00%)	2 / 819 (0.24%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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			
Haemoptysis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 819 (0.12%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Pyomyositis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	0 / 467 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 118 (0.00%)	0 / 819 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1/2: Etoricoxib 60 mg/60 mg	Part 1/2: Etoricoxib 60 mg/90 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 350 (1.14%)	5 / 363 (1.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 350 (0.29%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 350 (0.29%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 350 (0.29%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 350 (0.29%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyomyositis			
subjects affected / exposed	0 / 350 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 350 (0.00%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: Placebo	Part 1: Etoricoxib 60 mg	Part 1: Etoricoxib 90 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 118 (5.08%)	25 / 819 (3.05%)	17 / 467 (3.64%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 118 (5.08%)	25 / 819 (3.05%)	17 / 467 (3.64%)
occurrences (all)	8	27	27

Non-serious adverse events	Part 1/2: Etoricoxib 60 mg/60 mg	Part 1/2: Etoricoxib 60 mg/90 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 350 (1.71%)	6 / 363 (1.65%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 350 (1.71%)	6 / 363 (1.65%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported