Clinical trial results:
A Randomized, Double-Blind, Multicenter, Placebo- and active Comparator-Controlled Study to evaluate Efficacy and Safety of MR308 in the Treatment of Acute Pain After Abdominal Hysterectomy Surgery under General Anaesthesia (STARDOM2).

Summary

EudraCT number	2016-000593-38
Trial protocol	ES SK LV PL BG
Global end of trial date	29 June 2018

Results information

Result version number	v1 (current)
This version publication date	04 April 2019
First version publication date	04 April 2019

Trial information

Trial identification

Sponsor protocol code	MR308-3502

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd.
Sponsor organisation address	194-198 Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW
Public contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com
Scientific contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.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 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2018
Global end of trial reached?	Yes
Global end of trial date	29 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of MR308 doses in the treatment of acute moderate to severe pain. Efficacy was assessed by showing superiority of MR308 doses over placebo and non-inferiority compared with tramadol, followed by superiority over tramadol and superiority over celecoxib based on the Sum of Pain Intensity Differences over 0-4 hours (SPID4).

Protection of trial subjects:

Protection of trial subjects:
1) Inclusion criteria:
- If a female was of child-bearing potential, she had to use highly effective methods of contraception throughout the study, be not breastfeeding, and have negative pregnancy tests prior to receiving IMP.
- The subject had to be alert and calm, spontaneously payed attention to caregiver, e.g. Richmond Agitation–Sedation Scale (RASS) = 0 (Sessler et al., 2002 & Ely et al., 2003).
2) Exclusion criteria:
- Several exclusion criteria excluded subjects who were at risk from the use of IMP (e.g. those with hypersensitivity) or the study methods (please refer to protocol)
3) Dscontinuation:
The Investigator(s) or subjects themselves were able to stop study treatment at any time for safety or personal reasons.
The participation of an individual subject could be terminated prematurely if subjects were taking the maximum rescue medication dose of 4000 mg Paracetamol per day and still reported uncontrolled pain or if any condition ocurred which, in the opinion of the Investigator, no longer permitted a safe participation in the study.
4) Safety was assessed throughout the study by evaluation of the incidence of adverse events and clinically significant changes on laboratory safety results, vital signs, physical examination, and electrocardiograms (ECGs).

Background therapy:

Background therapy:
Paracetamol (Acetaminophen), taken orally, was the rescue pain medication during the Double-blind Period of the study.
The rescue medication was supplied to the subject with the IMP at randomisation and could be taken up to four times a day and the maximum daily dose of 4 g in divided doses up to Visit 8.
A single dose of rescue medication was defined as 1000 mg (two tablets). At the discretion of the Investigator, the paracetamol dose may have been lowered to 500 mg (1 tablet), if the Investigator or subject felt that the dose was higher than what may be required to provide adequate analgesic effect.

Evidence for comparator:

The new co-crystal MR308 combines two well-known active principles, tramadol and celecoxib. The analgesic effect is expected to occur at lower doses than those of the approved constituents drugs of MR308 (tramadol hydrochloride and celecoxib) for the treatment of acute pain. Therefore it was compared to both constituents, tramadol and celecoxib.

Actual start date of recruitment	01 December 2016
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: 272
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Bulgaria: 254
Country: Number of subjects enrolled	Hungary: 195
Country: Number of subjects enrolled	Latvia: 123
Country: Number of subjects enrolled	Belarus: 153
Country: Number of subjects enrolled	Russian Federation: 113
Worldwide total number of subjects	1138
EEA total number of subjects	872

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)	1093
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 65 sites in 7 countries: 5 sites in Belarus, 12 sites in Bulgaria, 13 sites in Hungary, 3 sites in Latvia, 11 sites in Poland, 11 sites in Russia and 10 sites in Spain. The first patient was recruited on 05-Apr-2017, the last visit of the last patient was on 29-Jun-2018.

Pre-assignment

Screening details:

The Screening Period may have taken up to 28 days. Subjects, who did not comply with all screening inclusion and exclusion criteria, withdrew their consent prior to the planned abdominal surgery (Visit 2) and all other subjects who discontinued the study before being randomised were considered Screening Failures.

Period 1

Period 1 title	Treatment Period/Double-Blind Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The test IMP MR308 tablets and tramadol capsules were over-encapsulated to have the same appearance. In order to maintain the blind, subjects randomised to MR308 and celecoxib treatment arms were given twice daily additional placebo capsules to match the posology of the active comparator, tramadol, which was given four times daily. Subjects randomised to any treatment arm (including placebo) took their study treatment four times daily.

Arms

Are arms mutually exclusive?	Yes
Arm title	MR308 100 mg

Arm description:

Subjects received MR308 100 mg (44 mg of tramadol hydrochloride and 56 mg of celecoxib) bid.

Arm type	Experimental
Investigational medicinal product name	Tramadol/Celecoxib 100 mg
Investigational medicinal product code	MR308 100 mg
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MR308 100 mg (44 mg of tramadol hydrochloride and 56 mg of celecoxib).
Subjects received two over-encapsulated tablets with active treatment and two placebo capsules daily.
Total daily dose: 200 mg MR308 (88 mg of tramadol hydrochloride and 112 mg of celecoxib).

Arm title	MR308 150 mg

Arm description:

Subects received MR308 150 mg (66 mg of tramadol hydrochloride and 84 mg of celecoxib) bid.

Arm type	Experimental
Investigational medicinal product name	Tramadol/Celecoxib 150 mg
Investigational medicinal product code	MR308 150 mg
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MR308 150 mg (66 mg of tramadol hydrochloride and 84 mg of celecoxib).
Subjects received two over-encapsulated tablets with active treatment and two placebo capsules daily.

Total daily dose: 300 mg MR308 (132 mg of tramadol hydrochloride and 168 mg of celecoxib).

Arm title	MR308 200 mg

Arm description:

Subjects received MR308 200 mg (88 mg of tramadol hydrochloride and 112 mg of celecoxib) bid.

Arm type	Experimental
Investigational medicinal product name	Tramadol/Celecoxib 200 mg
Investigational medicinal product code	MR308 200 mg
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MR308 200 mg (88 mg of tramadol hydrochloride and 112 mg of celecoxib).
Subjects received two over-encapsulated tablets with active treatment and two placebo capsules daily.
Total daily dose: 400 mg MR308 (176 mg of tramadol hydrochloride and 224 mg of celecoxib).

Arm title	Tramadol

Arm description:

Subjects received Tramadol 100 mg IR qid.

Arm type	Active comparator
Investigational medicinal product name	Tramadol 100 mg IR
Investigational medicinal product code	Tramadol 100 mg
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tramadol hydrochloride immediate release 100 mg.
Subjects received 4 over-encapsulated capsules with active treatment daily.
Total daily dose: 400 mg tramadol.

Arm title	Celecoxib

Arm description:

Subjects received Celecoxib 100 mg bid

Arm type	Active comparator
Investigational medicinal product name	Celecoxib 100 mg
Investigational medicinal product code	Celecoxib 100 mg
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Celecoxib 100 mg.
Subjects received one capsule of 100 mg celecoxib per intake for two times a day plus 2 intakes of placebo capsules to maintain the blind.
Total daily dose: 200 mg celecoxib.

Arm title	Placebo

Arm description:

Subjects receied placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 4 doses of placebo per day.

Number of subjects in period 1	MR308 100 mg	MR308 150 mg	MR308 200 mg
Started	207	207	208
Completed	195	197	196
Not completed	12	10	12
Consent withdrawn by subject	9	6	7
Adverse event, non-fatal	2	2	4
Non-compliance with study drug	-	-	-
Lack of efficacy	1	2	1
Protocol deviation	-	-	-

Number of subjects in period 1	Tramadol	Celecoxib	Placebo
Started	208	206	102
Completed	193	190	95
Not completed	15	16	7
Consent withdrawn by subject	8	11	5
Adverse event, non-fatal	6	4	1
Non-compliance with study drug	1	-	1
Lack of efficacy	-	-	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	MR308 100 mg
Reporting group description:	
Subjects received MR308 100 mg (44 mg of tramadol hydrochloride and 56 mg of celecoxib) bid.	
Reporting group title	MR308 150 mg
Reporting group description:	
Subects received MR308 150 mg (66 mg of tramadol hydrochloride and 84 mg of celecoxib) bid.	
Reporting group title	MR308 200 mg
Reporting group description:	
Subjects received MR308 200 mg (88 mg of tramadol hydrochloride and 112 mg of celecoxib) bid.	
Reporting group title	Tramadol
Reporting group description:	
Subjects received Tramadol 100 mg IR qid.	
Reporting group title	Celecoxib
Reporting group description:	
Subjects received Celecoxib 100 mg bid	
Reporting group title	Placebo
Reporting group description:	
Subjects receied placebo.	

Reporting group values	MR308 100 mg	MR308 150 mg	MR308 200 mg
Number of subjects	207	207	208
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	48.2	48.2	48.5
standard deviation	± 7.54	± 6.03	± 7.43
Gender categorical Units: Subjects			
Female	207	207	208
Male	0	0	0

Reporting group values	Tramadol	Celecoxib	Placebo
Number of subjects	208	206	102

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	48.7	48.1	48.7
standard deviation	± 7.51	± 6.25	± 7.13
Gender categorical Units: Subjects			
Female	208	206	102
Male	0	0	0

Reporting group values	Total		
Number of subjects	1138		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1138		
Male	0		

End points

End points reporting groups	
Reporting group title	MR308 100 mg
Reporting group description:	
Subjects received MR308 100 mg (44 mg of tramadol hydrochloride and 56 mg of celecoxib) bid.	
Reporting group title	MR308 150 mg
Reporting group description:	
Subects received MR308 150 mg (66 mg of tramadol hydrochloride and 84 mg of celecoxib) bid.	
Reporting group title	MR308 200 mg
Reporting group description:	
Subjects received MR308 200 mg (88 mg of tramadol hydrochloride and 112 mg of celecoxib) bid.	
Reporting group title	Tramadol
Reporting group description:	
Subjects received Tramadol 100 mg IR qid.	
Reporting group title	Celecoxib
Reporting group description:	
Subjects received Celecoxib 100 mg bid	
Reporting group title	Placebo
Reporting group description:	
Subjects receied placebo.	

Primary: SPID4	
End point title	SPID4
End point description:	
The primary efficacy endpoint was the SPID4. SPID4 is derived as the weighted Sum of Pain Intensity Differences (baseline pain – current pain), measured at different time points via the Pain Intensity - Visual Analogue Scale (PI-VAS, range of scores: 0-100 mm). Time between two consecutive measurements was used for weighting. Larger values indicate larger pain relief. LOCF imputation was employed.	
End point type	Primary
End point timeframe:	
Sum of pain intensity difference between baseline (pre-dose) and 4 hour post-dose.	

End point values	MR308 100 mg	MR308 150 mg	MR308 200 mg	Tramadol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207	207	208	208
Units: PI-VAS score				
arithmetic mean (standard deviation)	60.93 (± 67.265)	60.98 (± 65.302)	68.60 (± 66.589)	73.89 (± 74.174)

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	102		

Units: PI-VAS score				
arithmetic mean (standard deviation)	67.00 (± 71.900)	46.89 (± 62.080)		

Statistical analyses

Statistical analysis title	Superiority of MR308 100 mg over placebo

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 100 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.069 [2]
Method	ANCOVA

Notes:

[1] - Test for superiority of the MR308 dose over placebo regarding SPID4

[2] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 150 mg over placebo

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	Placebo v MR308 150 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.011 [4]
Method	ANCOVA

Notes:

[3] - Test for superiority of the MR308 dose over placebo regarding SPID4

[4] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 200 mg over placebo

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	Placebo v MR308 200 mg

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.003 [6]
Method	ANCOVA

Notes:

[5] - Test for superiority of the MR308 dose over placebo regarding SPID4

[6] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Non-inferiority of MR308 100 mg versus tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 100 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001 [8]
Method	ANCOVA

Notes:

[7] - Test for non-inferiority of the MR308 dose over placebo regarding SPID4

[8] - Raw P-value from one-sided test of non-inferiority for testing the Null Hypothesis that the differences of means is >=40mm*h

Statistical analysis title	Non-inferiority of MR308 150 mg versus tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 150 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	< 0.001 [10]
Method	ANCOVA

Notes:

[9] - Test for non-inferiority of the MR308 dose over placebo regarding SPID4

[10] - Raw P-value from one-sided test of non-inferiority for testing the Null Hypothesis that the differences of means is >=40mm*h

Statistical analysis title	Non-inferiority of MR308 200 mg versus tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 200 mg v Tramadol

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	ANCOVA

Notes:

[11] - Test for non-inferiority of the MR308 dose over placebo regarding SPID4

[12] - Raw P-value from one-sided test of non-inferiority for testing the Null Hypothesis that the differences of means is >=40mm*h

Statistical analysis title	Superiority of MR308 100 mg over tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 100 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.034 [14]
Method	ANCOVA

Notes:

[13] - Test for Superiority over tramadol regarding SPID4

[14] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 150 mg over tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 150 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.206 [16]
Method	ANCOVA

Notes:

[15] - Test for Superiority over tramadol regarding SPID4

[16] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 200 mg over tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 200 mg v Tramadol

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.385 [18]
Method	ANCOVA

Notes:

[17] - Test for Superiority over tramadol regarding SPID4

[18] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 100 mg over celecoxib

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	MR308 100 mg v Celecoxib
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.1 [20]
Method	ANCOVA

Notes:

[19] - Test for Superiority over celecoxib regarding SPID4

[20] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 150 mg over celecoxib

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	Celecoxib v MR308 150 mg
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.392 [22]
Method	ANCOVA

Notes:

[21] - Test for Superiority over celecoxib regarding SPID4

[22] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Statistical analysis title	Superiority of MR308 200 mg over celecoxib

Statistical analysis description:

The comparison of all MR308 doses with placebo, tramadol and celecoxib based on SPID4 was performed using an analysis of covariance (ANCOVA) model with treatment and QPI (moderate, severe) as fixed effects, centre as a random effect and pre-dose (0h) PI-VAS as covariate.
Covariance parameters were estimated via the restricted maximum likelihood method. An unstructured covariance matrix was assumed (common across all treatment arms) and the Kenward and Roger's method for fixed effects degrees

Comparison groups	Celecoxib v MR308 200 mg

Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.4 [24]
Method	ANCOVA

Notes:

[23] - Test for Superiority over celecoxib regarding SPID4

[24] - Raw P-value from one-sided test of superiority for testing the Null Hypothesis that the differences of means is >=0mm*h

Secondary: 50% responder at 4 hours

End point title	50% responder at 4 hours

End point description:

50% responder at 4 hours, defined as subjects with a reduction in pain intensity (PI-VAS) from 0 hours at 4 hours of at least 50%.

End point type	Secondary

End point timeframe:

Baseline to 4 hours after the first dose.

End point values	MR308 100 mg	MR308 150 mg	MR308 200 mg	Tramadol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207	207	208	208
Units: 50% Responders	48	51	64	64

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	102		
Units: 50% Responders	49	18		

Statistical analyses

Statistical analysis title	50% Responder MR308 100 mg vs placebo at 4 h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.423 [25]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	2.518

Notes:

[25] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 150 mg vs placebo at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Placebo v MR308 150 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.931
upper limit	3.431

Notes:

[26] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 200 mg vs placebo at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Placebo v MR308 200 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [27]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.148
upper limit	4.144

Notes:

[27] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 100 mg vs tramadol at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [28]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.448
upper limit	1.183

Notes:

[28] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 150 mg vs tramadol at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Tramadol v MR308 150 mg
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987 [29]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	1.605

Notes:

[29] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 200 mg vs tramadol at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Tramadol v MR308 200 mg

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.765
upper limit	1.933

Notes:

[30] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 100 mg vs celecoxib at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Celecoxib
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57 [31]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.525
upper limit	1.426

Notes:

[31] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 150 mg vs celecoxib at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Celecoxib v MR308 150 mg
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.721
upper limit	1.941

Notes:

[32] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Statistical analysis title	50% Responder MR308 200 mg vs celecoxib at 4h

Statistical analysis description:

The probability of being a 50% responder at 4h was analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Celecoxib v MR308 200 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 [33]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.895
upper limit	2.331

Notes:

[33] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1.

Secondary: Rescue medication during the first 4 hours

End point title	Rescue medication during the first 4 hours

End point description:

Use of at least one dose of rescue medication during the first 4 hours

End point type	Secondary

End point timeframe:

Baseline (pre-dose) to 4 hours post dose.

End point values	MR308 100 mg	MR308 150 mg	MR308 200 mg	Tramadol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207	207	208	208
Units: Number of subjects who used rescue medic	43	33	35	38

End point values	Celecoxib	Placebo		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	102		
Units: Number of subjects who used rescue medic	41	28		

Statistical analyses

Statistical analysis title	Use of RM in first 4h - 100 mg vs placebo

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.154

Notes:

[34] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 150 mg vs placebo

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Placebo v MR308 150 mg
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.231
upper limit	0.776

Notes:

[35] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

	Use of RM in first 4h - 200 mg vs placebo

Statistical analysis title	

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Placebo v MR308 200 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [36]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.887

Notes:

[36] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 100 mg vs tramadol

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Tramadol
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594 [37]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.688
upper limit	1.92

Notes:

[37] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 150 mg vs tramadol

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Tramadol v MR308 150 mg

Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306 [38]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.441
upper limit	1.294

Notes:

[38] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 200 mg vs tramadol

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Tramadol v MR308 200 mg
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6 [39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.476

Notes:

[39] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 100 mg vs celecoxib

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	MR308 100 mg v Celecoxib
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.794 [40]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.646
upper limit	1.769

Notes:

[40] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 150 mg vs celecoxib

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Celecoxib v MR308 150 mg
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193 [41]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.413
upper limit	1.196

Notes:

[41] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Statistical analysis title	Use of RM in first 4h - 200 mg vs celecoxib

Statistical analysis description:

The probability of using at least one dose of rescue medication during the first 4h were each analysed using respective logistic regression models with treatment and QPI group (moderate, severe) as fixed effects, centre (pooling) applied as necessary as random effect und pre-dose (0h) PI-VAS as covariate.

Comparison groups	Celecoxib v MR308 200 mg
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.423 [42]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	1.364

Notes:

[42] - P-value from two-sided test of no difference for testing the Null Hypothesis that the Odds Ratio is 1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs were collected from the time the informed consent was signed until the follow-up visit, which took place at least 7 days after the subject's last dose of IMP.	
Adverse event reporting additional description:	
AEs were recorded by non-elicited reporting at each study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	MR308 100 mg
Reporting group description:	
Subjects received MR308 100 mg (44 mg of tramadol hydrochloride and 56 mg of celecoxib) bid.	
Reporting group title	MR308 150 mg
Reporting group description:	
Subects received MR308 150 mg (66 mg of tramadol hydrochloride and 84 mg of celecoxib) bid.	
Reporting group title	MR308 200 mg
Reporting group description:	
Subjects received MR308 200 mg (88 mg of tramadol hydrochloride and 112 mg of celecoxib) bid.	
Reporting group title	Tramadol
Reporting group description:	
Subjects received Tramadol 100 mg IR qid.	
Reporting group title	Celecoxib
Reporting group description:	
Subjects received Celecoxib 100 mg bid	
Reporting group title	Placebo
Reporting group description:	
Subjects receied placebo.	

Serious adverse events	MR308 100 mg	MR308 150 mg	MR308 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 207 (0.97%)	3 / 205 (1.46%)	0 / 208 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Aponeurosis contusion			
subjects affected / exposed	0 / 207 (0.00%)	1 / 205 (0.49%)	0 / 208 (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
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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
Extravasation blood			
subjects affected / exposed	0 / 207 (0.00%)	1 / 205 (0.49%)	0 / 208 (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
Haematoma			
subjects affected / exposed	0 / 207 (0.00%)	1 / 205 (0.49%)	0 / 208 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 205 (0.00%)	0 / 208 (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
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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
Ileus			
subjects affected / exposed	1 / 207 (0.48%)	0 / 205 (0.00%)	0 / 208 (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
Intestinal obstruction			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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
Subileus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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

Vomiting			
subjects affected / exposed	0 / 207 (0.00%)	1 / 205 (0.49%)	0 / 208 (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
Abdominal wall abscess			
subjects affected / exposed	1 / 207 (0.48%)	0 / 205 (0.00%)	0 / 208 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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 colic			
subjects affected / exposed	0 / 207 (0.00%)	0 / 205 (0.00%)	0 / 208 (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

Serious adverse events	Tramadol	Celecoxib	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 208 (1.44%)	3 / 206 (1.46%)	0 / 102 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Aponeurosis contusion			
subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (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			
Deep vein thrombosis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 206 (0.00%)	0 / 102 (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
Extravasation blood			

subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (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
Haematoma			
subjects affected / exposed	0 / 208 (0.00%)	1 / 206 (0.49%)	0 / 102 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 206 (0.00%)	0 / 102 (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
Ileus			
subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (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
Intestinal obstruction			
subjects affected / exposed	0 / 208 (0.00%)	1 / 206 (0.49%)	0 / 102 (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
Subileus			
subjects affected / exposed	1 / 208 (0.48%)	0 / 206 (0.00%)	0 / 102 (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
Vomiting			
subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (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

Abdominal wall abscess			
subjects affected / exposed	0 / 208 (0.00%)	0 / 206 (0.00%)	0 / 102 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 208 (0.48%)	0 / 206 (0.00%)	0 / 102 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 208 (0.00%)	1 / 206 (0.49%)	0 / 102 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	MR308 100 mg	MR308 150 mg	MR308 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 207 (30.43%)	60 / 205 (29.27%)	62 / 208 (29.81%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 207 (1.93%)	6 / 205 (2.93%)	4 / 208 (1.92%)
occurrences (all)	4	6	4
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 207 (2.42%)	4 / 205 (1.95%)	3 / 208 (1.44%)
occurrences (all)	5	4	3
Nervous system disorders			
Somnolence			
subjects affected / exposed	11 / 207 (5.31%)	13 / 205 (6.34%)	13 / 208 (6.25%)
occurrences (all)	13	18	13
Dizziness			
subjects affected / exposed	7 / 207 (3.38%)	7 / 205 (3.41%)	7 / 208 (3.37%)
occurrences (all)	7	9	8
General disorders and administration			

site conditions			
Fatigue11			
subjects affected / exposed	11 / 207 (5.31%)	10 / 205 (4.88%)	8 / 208 (3.85%)
occurrences (all)	11	13	9
Pyrexia			
subjects affected / exposed	3 / 207 (1.45%)	5 / 205 (2.44%)	0 / 208 (0.00%)
occurrences (all)	3	5	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 207 (0.97%)	4 / 205 (1.95%)	6 / 208 (2.88%)
occurrences (all)	2	4	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 207 (3.38%)	7 / 205 (3.41%)	9 / 208 (4.33%)
occurrences (all)	7	7	9
Constipation			
subjects affected / exposed	10 / 207 (4.83%)	12 / 205 (5.85%)	10 / 208 (4.81%)
occurrences (all)	10	12	10
Vomiting			
subjects affected / exposed	2 / 207 (0.97%)	7 / 205 (3.41%)	7 / 208 (3.37%)
occurrences (all)	5	7	8
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 207 (0.97%)	3 / 205 (1.46%)	4 / 208 (1.92%)
occurrences (all)	2	4	7

Non-serious adverse events	Tramadol	Celecoxib	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 208 (39.42%)	67 / 206 (32.52%)	30 / 102 (29.41%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 208 (4.33%)	8 / 206 (3.88%)	1 / 102 (0.98%)
occurrences (all)	9	8	1
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 208 (2.88%)	6 / 206 (2.91%)	1 / 102 (0.98%)
occurrences (all)	6	6	1
Nervous system disorders			

Somnolence			
subjects affected / exposed	22 / 208 (10.58%)	8 / 206 (3.88%)	8 / 102 (7.84%)
occurrences (all)	23	11	10
Dizziness			
subjects affected / exposed	12 / 208 (5.77%)	5 / 206 (2.43%)	5 / 102 (4.90%)
occurrences (all)	13	6	6
General disorders and administration site conditions			
Fatigue11			
subjects affected / exposed	6 / 208 (2.88%)	12 / 206 (5.83%)	9 / 102 (8.82%)
occurrences (all)	6	14	11
Pyrexia			
subjects affected / exposed	0 / 208 (0.00%)	6 / 206 (2.91%)	2 / 102 (1.96%)
occurrences (all)	0	6	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 208 (2.40%)	3 / 206 (1.46%)	1 / 102 (0.98%)
occurrences (all)	5	3	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	30 / 208 (14.42%)	14 / 206 (6.80%)	9 / 102 (8.82%)
occurrences (all)	35	16	9
Constipation			
subjects affected / exposed	22 / 208 (10.58%)	6 / 206 (2.91%)	5 / 102 (4.90%)
occurrences (all)	25	7	5
Vomiting			
subjects affected / exposed	16 / 208 (7.69%)	11 / 206 (5.34%)	4 / 102 (3.92%)
occurrences (all)	22	11	8
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 208 (2.88%)	3 / 206 (1.46%)	2 / 102 (1.96%)
occurrences (all)	6	3	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2017	The Protocol Amendment introduced changes following clarification from the European Medicines Agency (EMA) that the study is required to have confirmatory testing against the celecoxib arm, unlike the exploratory analysis that was planned in the original protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported