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 Third Molar Tooth Extraction (STARDOM1).

Summary

EudraCT number	2016-000592-24
Trial protocol	DE PL IT
Global end of trial date	04 January 2018

Results information

Result version number	v1 (current)
This version publication date	18 January 2019
First version publication date	18 January 2019

Trial information

Trial identification

Sponsor protocol code	MR308-3501

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	04 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2018
Global end of trial reached?	Yes
Global end of trial date	04 January 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 based on the sum of pain intesity differences over 0-4 hours (SPID4).

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 was 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:

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 5.
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 tramadol, the opiod component in MR308.

Actual start date of recruitment	28 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	Canada: 11
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Poland: 394
Country: Number of subjects enrolled	Spain: 192
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Hungary: 89
Worldwide total number of subjects	726
EEA total number of subjects	715

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)	725
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 31 sites in 6 countries: 3 sites in Canada, 3 sites in Germany, 4 sites in Hungary, 1 site in Italy, 10 sites in Poland and 9 sites in Spain. First patient first visit was 28-Dec-2016, last patient last visit was 04-Jan-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 third molar extractions (Visit 2) and all other subjects who discontinued the study before being randomised were considered Screening Failures.

Pre-assignment period milestones

Number of subjects started	887[1]
Number of subjects completed	726

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 9
Reason: Number of subjects	Consent withdrawn by subject: 53
Reason: Number of subjects	Failed procedures: 73
Reason: Number of subjects	Lost to follow up: 15
Reason: Number of subjects	Administrative: 11

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Age stratification and subjects per-country were only analysed for randomised subjects.

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 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	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	164	160	160
Completed	161	152	153
Not completed	3	8	7
Consent withdrawn by subject	2	4	4
Administrative	-	1	-
Adverse event, non-fatal	1	3	3

Number of subjects in period 1	Tramadol	Placebo
Started	159	83
Completed	138	81
Not completed	21	2
Consent withdrawn by subject	9	2
Administrative	-	-
Adverse event, non-fatal	12	-

Baseline characteristics

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	Placebo
Reporting group description:	
Subjects receied placebo.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as all randomised subjects. The ITT population was analysed according to the treatment arm in which the subject was randomised.	

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	163	160	160	158
Units: PI-VAS score				
arithmetic mean (standard deviation)	60.61 (± 98.177)	64.15 (± 94.870)	66.17 (± 99.569)	23.45 (± 81.731)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	83			

Units: PI-VAS score				
arithmetic mean (standard deviation)	-9.12 (± 69.388)			

Statistical analyses

Statistical analysis title	Superiority of MR308 100 mg over placebo

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	Placebo v MR308 100 mg
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [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	Non-inferiority of MR308 100 mg versus tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	MR308 100 mg v Tramadol
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	ANCOVA

Notes:

[3] - Test for non-inferiority versus tramadol (NI-margin of 40mm*h) regarding SPID4

[4] - 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 and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	MR308 100 mg v Tramadol

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	ANCOVA

Notes:

[5] - Test for : Superiority over tramadol 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	Superiority of MR308 150 mg over placebo

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	MR308 150 mg v MR308 200 mg v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	ANCOVA

Notes:

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

[8] - 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 and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	MR308 200 mg v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	ANCOVA

Notes:

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

[10] - 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 150 mg versus tra

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	Tramadol v MR308 150 mg

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	ANCOVA

Notes:

[11] - Test for non-inferiority versus tramadol (NI-margin of 40mm*h) 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	Non-inferiority of MR308 200 mg versus tra

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	Tramadol v MR308 200 mg
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.001 [14]
Method	ANCOVA

Notes:

[13] - Test for non-inferiority versus tramadol (NI-margin of 40mm*h) regarding SPID4

[14] - 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 150 mg over tramadol

Statistical analysis description:

The comparison of all MR308 doses with placebo and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	Tramadol v MR308 150 mg
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [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 and tramadol based on SPID4 was performed using an analysis of covariance 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 of freedom was used.

Comparison groups	Tramadol v MR308 200 mg

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001 [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

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	163	160	160	158
Units: Number of subjects	54	54	65	32

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Number of subjects	6			

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	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	17.296

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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.879
upper limit	17.57

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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.125
upper limit	25.061

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	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.143
upper limit	3.217

Statistical analysis title	50% Responder MR308 150 mg vs tramadol 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	Tramadol v MR308 150 mg
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	3.274

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	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.673
upper limit	4.642

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 first I;P 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	163	160	160	158
Units: Number of subjects who used rescue medic	67	71	63	89

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Number of subjects who used rescue medic	66			

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	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.091
upper limit	0.32

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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	0.367

Statistical analysis title	Use of RM in first 4h - 200 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 200 mg
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.286

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	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.359
upper limit	0.887

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	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.411
upper limit	1.017

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	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.319
upper limit	0.793

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	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	0 / 164 (0.00%)	0 / 159 (0.00%)	0 / 160 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 164 (0.00%)	0 / 159 (0.00%)	0 / 160 (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	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 160 (0.63%)	0 / 83 (0.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 160 (0.63%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	MR308 100 mg	MR308 150 mg	MR308 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 164 (73.17%)	119 / 159 (74.84%)	132 / 160 (82.50%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	46 / 164 (28.05%)	48 / 159 (30.19%)	61 / 160 (38.13%)
occurrences (all)	54	59	75
Disturbance in attention			
subjects affected / exposed	27 / 164 (16.46%)	25 / 159 (15.72%)	39 / 160 (24.38%)
occurrences (all)	31	26	51
Confusional state			
subjects affected / exposed	11 / 164 (6.71%)	9 / 159 (5.66%)	17 / 160 (10.63%)
occurrences (all)	14	11	20
Headache			
subjects affected / exposed	7 / 164 (4.27%)	3 / 159 (1.89%)	2 / 160 (1.25%)
occurrences (all)	8	4	2
General disorders and administration site conditions			
Somnolence			
subjects affected / exposed	75 / 164 (45.73%)	83 / 159 (52.20%)	105 / 160 (65.63%)
occurrences (all)	89	100	147
Fatigue			
subjects affected / exposed	54 / 164 (32.93%)	54 / 159 (33.96%)	66 / 160 (41.25%)
occurrences (all)	64	67	92
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	48 / 164 (29.27%)	47 / 159 (29.56%)	50 / 160 (31.25%)
occurrences (all)	55	63	67
Vomiting			
subjects affected / exposed	40 / 164 (24.39%)	32 / 159 (20.13%)	36 / 160 (22.50%)
occurrences (all)	47	37	45
Constipation			
subjects affected / exposed	11 / 164 (6.71%)	12 / 159 (7.55%)	17 / 160 (10.63%)
occurrences (all)	11	12	17
Retching			
subjects affected / exposed	2 / 164 (1.22%)	4 / 159 (2.52%)	4 / 160 (2.50%)
occurrences (all)	2	4	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 164 (2.44%)	18 / 159 (11.32%)	26 / 160 (16.25%)
occurrences (all)	4	19	28
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 164 (0.61%)	5 / 159 (3.14%)	13 / 160 (8.13%)
occurrences (all)	1	9	16

Non-serious adverse events	Tramadol	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 160 (85.63%)	49 / 83 (59.04%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	90 / 160 (56.25%)	12 / 83 (14.46%)	
occurrences (all)	116	12	
Disturbance in attention			
subjects affected / exposed	51 / 160 (31.88%)	16 / 83 (19.28%)	
occurrences (all)	73	16	
Confusional state			
subjects affected / exposed	30 / 160 (18.75%)	8 / 83 (9.64%)	
occurrences (all)	41	9	
Headache			
subjects affected / exposed	9 / 160 (5.63%)	1 / 83 (1.20%)	
occurrences (all)	10	1	
General disorders and administration site conditions			

Somnolence			
subjects affected / exposed	101 / 160 (63.13%)	31 / 83 (37.35%)	
occurrences (all)	147	38	
Fatigue			
subjects affected / exposed	72 / 160 (45.00%)	26 / 83 (31.33%)	
occurrences (all)	108	29	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	90 / 160 (56.25%)	15 / 83 (18.07%)	
occurrences (all)	109	16	
Vomiting			
subjects affected / exposed	88 / 160 (55.00%)	9 / 83 (10.84%)	
occurrences (all)	105	11	
Constipation			
subjects affected / exposed	28 / 160 (17.50%)	4 / 83 (4.82%)	
occurrences (all)	31	5	
Retching			
subjects affected / exposed	13 / 160 (8.13%)	2 / 83 (2.41%)	
occurrences (all)	13	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	44 / 160 (27.50%)	3 / 83 (3.61%)	
occurrences (all)	53	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	34 / 160 (21.25%)	2 / 83 (2.41%)	
occurrences (all)	40	2	

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