Clinical trial results:
A randomized, double-blind, placebo-controlled, 4-way cross-over, multiple dose study to investigate the analgesic effects of buprenorphine and minacipran in healthy volunteers

Summary

EudraCT number	2012-002302-43
Trial protocol	NL
Global end of trial date	04 October 2012

Results information

Result version number	v1 (current)
This version publication date	24 June 2022
First version publication date	24 June 2022

Trial information

Trial identification

Sponsor protocol code	DFP-06/CD/001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Reddy's Laboratories Limited
Sponsor organisation address	8-2-337 Road no. 3, Banjara Hills , Hyderabad, India, 500034
Public contact	Geert Jan Groeneveld, Cente for Human Drug Research, 31 715246400, GGroeneveld@chdr.nl
Scientific contact	Geert Jan Groeneveld, Cente for Human Drug Research, 31 715246400, GGroeneveld@chdr.nl

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	20 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2012
Global end of trial reached?	Yes
Global end of trial date	04 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine if the analgesic effects of co-administration of a single oral dose of milnacipran with a single intravenous dose of buprenorphine were higher than those of buprenorphine alone (potentiation) or higher than those of buprenorphine alone plus milnacipran alone (synergy) in healthy subjects.
2. To determine if the analgesic effects of co-administration of 8 days of milnacipran bid in combination with a single administration of buprenorphine were higher than those of buprenorphine alone (potentiation) or higher than those of buprenorphine alone plus multiple doses of milnacipran alone (synergy) in healthy subjects.
3. To investigate the safety and tolerability of co-administration of intravenous buprenorphine and oral milnacipran in healthy subjects.
4. To examine the potential pharmacokinetic interactions between intravenous buprenorphine and oral milnacipran in healthy subjects.

Protection of trial subjects:

Subjects were given an oral and written explanation about the study. Only after they had given written acknowledgement of informed consent to participate did any trial-related procedure take place. All informed consent forms were signed in duplicate by the subject and the investigator or his delegate, with one original being retained at the investigational site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2012
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	Netherlands: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were recruited from CHDR volunteer database. The subjects were recruited after screening on the basis of inclusion and exclusion criteria as defined in the study protocol.

Pre-assignment

Screening details:

The subjects were screened on the basis of inclusion and exclusion criteria as defined in the protocol.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Buprenorphine placebo+ Milnacipran 50 mg

Arm description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Arm type	Experimental
Investigational medicinal product name	Buprenorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Investigational medicinal product name	Milnacipran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily

Arm title	Buprenorphine active+ Milnacipran 25 mg

Arm description:

Buprenorphine was administered on Day 1 and Day 8 and in three different doses: first a 30 minutes 0.5 µg/kg sub-therapeutic infusion followed 1.5 hours later by a second 30 minutes 1 µg/kg minimally-therapeutic infusion followed 1.5 hours later by the last 30 minutes 3 µg/kg therapeutic infusion. Milnacipran was administered twice daily (bid)

Arm type	Experimental

Investigational medicinal product name	Buprenorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Investigational medicinal product name	Milnacipran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily

Arm title	Buprenorphine active+ Milnacipran 50 mg

Arm description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Arm type	Experimental
Investigational medicinal product name	Buprenorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Investigational medicinal product name	Milnacipran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily

Arm title	Buprenorphine active+ Milnacipran placebo

Arm description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Arm type	Experimental
Investigational medicinal product name	Buprenorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).

C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Investigational medicinal product name	Milnacipran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily

Number of subjects in period 1	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg
Started	11	9	10
Completed	10	9	9
Not completed	1	0	1
Consent withdrawn by subject	1	-	1

Number of subjects in period 1	Buprenorphine active+ Milnacipran placebo
Started	10
Completed	10
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	11	11	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.2		
standard deviation	± 3.5	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	11	11	

End points

End points reporting groups

Reporting group title	Buprenorphine placebo+ Milnacipran 50 mg
Reporting group description:	
Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows: A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose). B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose). C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).	
Reporting group title	Buprenorphine active+ Milnacipran 25 mg
Reporting group description:	
Buprenorphine was administered on Day 1 and Day 8 and in three different doses: first a 30 minutes 0.5 µg/kg sub-therapeutic infusion followed 1.5 hours later by a second 30 minutes 1 µg/kg minimally-therapeutic infusion followed 1.5 hours later by the last 30 minutes 3 µg/kg therapeutic infusion. Milnacipran was administered twice daily (bid)	
Reporting group title	Buprenorphine active+ Milnacipran 50 mg
Reporting group description:	
Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows: A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose). B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose). C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).	
Reporting group title	Buprenorphine active+ Milnacipran placebo
Reporting group description:	
Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows: A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose). B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose). C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-25 after first bump
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine +Milnacipran placebo and Buprenorphine + Milnacipran 25 mg	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-25 after second bump
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnacipran placebo and Buprenorphine+ Milnacipran 25 mg after second infusion of Buprenorphine	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-25 after third bump
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnapracin placebo and Buprenorphine+ Milnapracin 25 mg after third infusion of Buprenorphine	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-25
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine + Milnacipran placebo and Buprenorphine+ Milnacipran 25 mg	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-50
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnacipran placebo and Buprenorphine+ Milnacipran 50 mg	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-50 after first bump
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnacipran placebo and Buprenorphine+ Milnacipran 50 mg after first infusion of Buprenorphine	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-50 after second bump

Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnacipran placebo and Buprenorphine+ Milnacipran 50 mg after second infusion of Buprenorphine	
Subject analysis set title	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of Buprenorphine+ Milnacipran placebo and Buprenorphine+ Milnacipran 25 mg after third infusion of Buprenorphine	
Subject analysis set title	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of treatments: (BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	
Subject analysis set title	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of treatments: (BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 after first infusion of Buprenorphine	
Subject analysis set title	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of treatments: (BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 after second infusion of Buprenorphine	
Subject analysis set title	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of treatments: (BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 after third infusion of Buprenorphine	

Primary: Milnacipran AUC (0-t)- Day 1

End point title	Milnacipran AUC (0-t)- Day 1[1][2]
End point description:	
End point type	Primary
End point timeframe:	
AUC measured on administration of Milnacipran on Day 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	10	
Units: ng.hr/mL				
arithmetic mean (standard deviation)	696.50 (± 160.60)	318.10 (± 102.30)	633.00 (± 154.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Milnacipran tmax- Day 1

End point title	Milnacipran tmax- Day 1[3][4]

End point description:

End point type	Primary

End point timeframe:

Time to reach maximum plasma concentration (Cmax) on Day 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	10	
Units: hour				
arithmetic mean (standard deviation)	3.156 (± 0.6175)	3.204 (± 0.8491)	3.17 (± 1.05)	

Statistical analyses

No statistical analyses for this end point

Primary: Milnacipran Cmax- Day 1

End point title	Milnacipran Cmax- Day 1[5][6]

End point description:

End point type	Primary

End point timeframe:

Cmax measured on Day 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	10	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	105.20 (± 26.93)	46.92 (± 15.92)	99.81 (± 37.20)	

Statistical analyses

No statistical analyses for this end point

Primary: Milnacipran AUC (0-t)- Day 8

End point title	Milnacipran AUC (0-t)- Day 8[7][8]

End point description:

End point type	Primary

End point timeframe:

Area under the curve (AUC (0-t)) on day 8

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	9	
Units: ng.hr/mL				
arithmetic mean (standard deviation)	1281.0 (± 178.60)	629.20 (± 94.10)	1251.0 (± 306.70)	

Statistical analyses

No statistical analyses for this end point

Primary: Milnacipran tmax- Day 8

End point title	Milnacipran tmax- Day 8[9][10]

End point description:

End point type	Primary

End point timeframe:

Time taken to reach Cmax measured on Day 8 of the clinical trial

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	9	
Units: hour				
arithmetic mean (standard deviation)	1.845 (± 1.02)	2.646 (± 0.4848)	3.104 (± 0.9775)	

Statistical analyses

No statistical analyses for this end point

Primary: Milnacipran Cmax- Day 8

End point title	Milnacipran Cmax- Day 8[11][12]

End point description:

End point type	Primary

End point timeframe:

Milnacipran Cmax measured on Day 8 of the study

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Milnacipran Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	9	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	201.20 (± 58.51)	93.840 (± 11.69)	188.30 (± 66.65)	

Statistical analyses

No statistical analyses for this end point

Primary: Buprenorphine Cmax after final IV infusion- Day 1

End point title	Buprenorphine Cmax after final IV infusion- Day 1[13][14]

End point description:

End point type	Primary

End point timeframe:

Cmax after 3rd IV infusion on Day 1

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Buprenorphine Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	0.375 (± 0.0197)	0.348 (± 0.0785)	0.369 (± 0.0566)	

Statistical analyses

No statistical analyses for this end point

Primary: Buprenorphine Cmax after final IV infusion- Day 8

End point title	Buprenorphine Cmax after final IV infusion- Day 8[15][16]

End point description:

End point type	Primary

End point timeframe:

Cmax after final infusion of Buprenorphine on Day 8

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analysis has not been specified because the study population is small.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point for all baseline period arm is not reported as Buprenorphine Placebo is administered to the subjects in one of the arms.

End point values	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	0.355 (± 0.0534)	0.389 (± 0.0720)	0.374 (± 0.0586)	

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of electrical repeat pain AUC- DAY 1

End point title	Estimate of difference of electrical repeat pain AUC- DAY 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	272	-242	621	217

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				

number (not applicable)	-92	-137	-455	317

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	446	514	93	729

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of electrical repeat pain AUC- DAY 8

End point title	Estimate of difference of electrical repeat pain AUC- DAY 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-381	-90	-54	-175

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-1394	-1509	-1424	-1249

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-860	-1118	-693	-769

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of electrical single pain AUC- DAY 1

End point title	Estimate of difference of electrical single pain AUC- DAY 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-84	-10	232	46

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-226	-273	-266	-138

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11		11
Units: mm.mA				
number (not applicable)	-95	-256	-100	72

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of electrical single pain AUC- DAY 8

End point title	Estimate of difference of electrical single pain AUC- DAY 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-59	-132	13	-59

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-341	-364	-290	-368

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-28	-101	20	-3

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of pressure pain AUC- DAY 1

End point title	Estimate of difference of pressure pain AUC- DAY 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	173	-696	-531	-352

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-324	50	-658	-362

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	117	425	-301	227

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of pressure pain AUC- DAY 8

End point title	Estimate of difference of pressure pain AUC- DAY 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.kPa				
number (not applicable)	-321	-830	316	-278

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.kPa				
number (not applicable)	9	-175	-339	542

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.kPa				
number (not applicable)	160	559	-787	707

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of cold pressor pain AUC- DAY 1

End point title	Estimate of difference of cold pressor pain AUC- DAY 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	113	290	-513	-36

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	60	173	464	-455

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	335	479	697	-170

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of cold pressor pain AUC- DAY 8

End point title	Estimate of difference of cold pressor pain AUC- DAY 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	554	705	415	558

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	641	704	751	468

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.s				
number (not applicable)	601	547	691	566

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of delta electrical single pain AUC- DAY 1

End point title	Estimate of difference of delta electrical single pain AUC- DAY 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	49.51	29.91	82.15	53.86

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	53.86	197.35	55.89	-91.64

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	-101.5	259.20	-290.4	-273.2

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference of delta electrical single pain AUC- DAY 8

End point title	Estimate of difference of delta electrical single pain AUC- DAY 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	23.34	245.53	71.73	113.54

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	60.88	-43.52	64.15	162.00

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm.mA				
number (not applicable)	104.58	-3.20	139.72	177.21

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Left Pupil/Iris Ratio- Day 1

End point title	Estimate of difference- Left Pupil/Iris Ratio- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.020	0.028	-0.013	-0.007

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.018	0.019	0.002	0.033

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11		11
Units: units				
number (not applicable)	0.028	0.022	0.024	0.039

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Left Pupil/Iris Ratio- Day 8

End point title	Estimate of difference- Left Pupil/Iris Ratio- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	-0.115	0.065	-0.029	-0.070

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	-0.048	-0.077	-0.047	-0.018

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.028	0.004	0.030	0.050

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Right Pupil/Iris Ratio- Day 1

End point title	Estimate of difference- Right Pupil/Iris Ratio- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.016	0.017	-0.016	-0.005

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.015	0.016	0.007	0.024

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.021	0.015	0.020	0.026

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Right Pupil/Iris Ratio- Day 8

End point title	Estimate of difference- Right Pupil/Iris Ratio- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	-0.128	-0.054	-0.032	-0.072

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	-0.052	-0.097	-0.043	-0.015

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: units				
number (not applicable)	0.016	-0.028	0.030	0.047

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic Inaccuracy - Day 1

End point title	Estimate of difference- Saccadic Inaccuracy - Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	0.1	-0.5	-0.2	-0.2

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	1.2	1.4	2.1	0

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	2.1	2.3	3.0	1.1

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic Inaccuracy - Day 8

End point title	Estimate of difference- Saccadic Inaccuracy - Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	0.5	0.2	1.6	0.8

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	0.4	0.3	-0.2	1.2

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	0.5	0.3	0.2	1.1

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic peak velocity- Day 1

End point title	Estimate of difference- Saccadic peak velocity- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	-22.0	-13.6	-45.4	-27.0

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	-39.0	-8.7	-55.6	-52.8

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	-56.5	-16.3	-68.1	-85.0

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic peak velocity- Day 8

End point title	Estimate of difference- Saccadic peak velocity- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	-27.8	24.1	-9.0	-4.2

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	9.5	-18.3	32.7	14.2

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: degree/second				
number (not applicable)	13.9	-19.6	31.9	29.5

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic reaction time- Day 1

End point title	Estimate of difference- Saccadic reaction time- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on day 1, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	-0.003	0.002	0.024	0.008

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	0.007	0.004	-0.002	0.020

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	0.013	0.005	0.006	0.028

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Saccadic reaction time- Day 8

End point title	Estimate of difference- Saccadic reaction time- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on day 8, over approximately 5 hours following study drug/placebo administration

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	0.003	-0.012	-0.004	-0.004

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	0.004	0.003	-0.013	0.021

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: second				
number (not applicable)	0.012	0.012	-0.006	0.029

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Adaptive tracking- Day 1

End point title	Estimate of difference- Adaptive tracking- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on Day 1 approximately for over 5 hours following the administration of drug/placebo

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	0.51	-0.15	-3.60	-1.08

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	-0.32	2.80	-2.90	-0.88

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	-0.72	2.15	-2.99	-1.33

Statistical analyses

No statistical analyses for this end point

Secondary: Estimate of difference- Adaptive tracking- Day 8

End point title	Estimate of difference- Adaptive tracking- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on Day 8 approximately for over 5 hours following the administration of drug/placebo

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	-0.50	-0.07	1.48	-0.68

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	-1.56	0.47	-1.92	-3.22

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: percent				
number (not applicable)	-1.56	1.24	-3.43	-2.49

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Estimate of difference- log transformed body sway- Day 1

End point title	Percent Estimate of difference- log transformed body sway- Day 1

End point description:

End point type	Secondary

End point timeframe:

Measured on Day 1 approximately for over 5 hours following the administration of drug/placebo

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	12.6	7.8	22.6	14.2

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	10.8	-9.5	34.3	11.9

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	25.2	8.2	54.6	17.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Estimate of difference- log transformed body sway- Day 8

End point title	Percent Estimate of difference- log transformed body sway- Day 8

End point description:

End point type	Secondary

End point timeframe:

Measured on Day 8 approximately for over 5 hours following the administration of drug/placebo

End point values	BUP+MIL-P vs BUP+MIL-25 after first bump	BUP+MIL-P vs BUP+MIL-25 after second bump	BUP+MIL-P vs BUP+MIL-25 after third bump	BUP+MIL-P vs BUP+MIL-25
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	6.3	17.2	15.4	12.9

End point values	BUP+MIL-P vs BUP+MIL-50	BUP+MIL-P vs BUP+MIL-50 after first bump	BUP+MIL-P vs BUP+MIL-50 after second bump	BUP+MIL-P vs BUP+MIL-50 after third bump
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	-2.4	-11.8	5.7	-0.3

End point values	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at first infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 2nd infusion	(BUP+MIL-P)+(BUP-P+MIL-50)-PRE vs BUP+MIL-50 at 3rd infusion
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: mm				
number (not applicable)	-4.1	-17.1	3.5	2.9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for adverse event reporting was throughout the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Buprenorphine placebo+ Milnacipran 50 mg

Reporting group description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Reporting group title	Buprenorphine active+ Milnacipran 25 mg

Reporting group description:

Buprenorphine was administered on Day 1 and Day 8 and in three different doses: first a 30 minutes 0.5 µg/kg sub-therapeutic infusion followed 1.5 hours later by a second 30 minutes 1 µg/kg minimally-therapeutic infusion followed 1.5 hours later by the last 30 minutes 3 µg/kg therapeutic infusion. Milnacipran was administered twice daily (bid)

Reporting group title	Buprenorphine active+ Milnacipran 50 mg

Reporting group description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Reporting group title	Buprenorphine active+ Milnacipran placebo

Reporting group description:

Milnacipran was administered twice daily. 3 different doses of Buprenorphine were used as follows:
A. First 30 minute infusion: 0.5 µg/kg (sub-therapeutic dose).
B. Second 30 minute infusion: 1 µg/kg (minimum therapeutic dose).
C. Third 30 minute infusion: 3 µg/kg (clinically relevant therapeutic dose).

Serious adverse events	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Buprenorphine active+ Milnacipran placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events			

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

Non-serious adverse events	Buprenorphine placebo+ Milnacipran 50 mg	Buprenorphine active+ Milnacipran 25 mg	Buprenorphine active+ Milnacipran 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	9 / 9 (100.00%)	10 / 10 (100.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Chest discomfort			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	6 / 9 (66.67%)	7 / 10 (70.00%)
occurrences (all)	3	6	7
Feeling cold			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Feeling drunk			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Feeling hot			
subjects affected / exposed	3 / 11 (27.27%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Feeling of relaxation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	2 / 11 (18.18%)	3 / 9 (33.33%)	2 / 10 (20.00%)
occurrences (all)	2	3	2
Hyperhidrosis			

subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	2	1	2
Malaise			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Ejaculation delayed			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Testicular pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Bradyphrenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Daydreaming			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Delusional perception			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Disinhibition			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Inappropriate affect			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Initial insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Heart rate increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Bradyphrenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 11 (18.18%)	6 / 9 (66.67%)	7 / 10 (70.00%)
occurrences (all)	2	6	7
Dizziness postural			

subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Dyskinesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 11 (36.36%)	4 / 9 (44.44%)	6 / 10 (60.00%)
occurrences (all)	4	4	6
Paraesthesia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Photophobia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Restlessness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	7 / 11 (63.64%)	8 / 9 (88.89%)	8 / 10 (80.00%)
occurrences (all)	7	8	8
Speech disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Accommodation disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 11 (9.09%)	2 / 9 (22.22%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Dry throat			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Epigastric discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	8 / 11 (72.73%)	8 / 9 (88.89%)	7 / 10 (70.00%)
occurrences (all)	8	8	7
Salivary hypersecretion			

subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	3 / 11 (27.27%)	6 / 9 (66.67%)	10 / 10 (100.00%)
occurrences (all)	3	6	10
Skin and subcutaneous tissue disorders			
Piloerection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	2 / 9 (22.22%)	2 / 10 (20.00%)
occurrences (all)	1	2	2
Pruritus generalized			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urinary hesitation			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Buprenorphine active+ Milnacipran placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Feeling cold			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Feeling drunk			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Feeling of relaxation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Thirst			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Ejaculation delayed			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Testicular pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oropharyngeal discomfort			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Bradyphrenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Daydreaming			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Delusional perception			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Disinhibition			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Inappropriate affect			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Initial insomnia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Investigations			
Heart rate increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	1		
Nervous system disorders			
Bradyphrenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	6		
Dizziness postural			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyskinesia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	8 / 10 (80.00%)		
occurrences (all)	8		
Speech disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Accommodation disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Constipation			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Dry throat			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	9 / 10 (90.00%)		
occurrences (all)	9		
Salivary hypersecretion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	7 / 10 (70.00%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			

Piloerection subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Pruritus generalized subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 3 / 10 (30.00%) 3 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Renal and urinary disorders Bladder spasm subjects affected / exposed occurrences (all) Dysuria subjects affected / exposed occurrences (all) Urinary hesitation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

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