Clinical trial results:
An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCL ER Tablets in Prurigo Nodularis Patients.

Summary

EudraCT number	2013-005628-41
Trial protocol	DE PL AT
Global end of trial date	26 July 2017

Results information

Result version number	v1 (current)
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	TR03ext

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174432
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trevi Therapeutics, Inc
Sponsor organisation address	195 Church Street, 14th Floor, New Haven, United States, CT 06510 USA
Public contact	Clinical Trial Information, Trevi Therapeutics, Inc., +1 203304-2499, Thomas.Sciascia@trevitherapeutics.com
Scientific contact	Clinical Trial Information, Trevi Therapeutics, Inc., +1 203304-2499, Thomas.Sciascia@trevitherapeutics.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	03 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2017
Global end of trial reached?	Yes
Global end of trial date	26 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of nalbuphine HCL ER tablets during a drug treatment period of up to 50 weeks.

Protection of trial subjects:

The first dosing day was on either Visit 1a or Visit 1b. Titration was based on tolerability. If the subject was experiencing a study drug-related AE or an AE that may have been aggravated by study drug up-titration, the study drug dose was not increased, regardless of the NRS score.

Any subject whose condition significantly changed after entering the study was carefully evaluated by the investigator and discussed with the medical monitor. Such subjects were to have been withdrawn from the study if continuing in the study would have placed them at risk or would have compromised the results of the study. Subjects who prematurely discontinued from the study were asked to undergo and complete early termination visit procedures and evaluations that may have been necessary to ensure that the subject was free of untoward effects and were asked to seek appropriate follow-up for any continuing problems.

This single-arm, open-label study provides descriptive data on a modest cohort of subjects with PN that is unique for the prolonged duration of observed therapy.

Background therapy:

There is no approved therapy for Prurigo Nodularis (PN) related pruritus in the United States or Europe. If Nalbuphine proves to be effective, PN patients could potentially benefit from this approach to treatment.

Patients were allowed to receive all clinically indicated medications during the study with the exceptions noted in the study protocol. Rescue Anti-Pruritic Medications: Concomitant use of medications for pruritus (including prior medications that are ongoing and remain at the same dose and dosing frequency following randomization) was not prohibited except as described in the protocol.

Evidence for comparator:

This extension study was open-label and the subjects were not randomly assigned to a particular study treatment. They continued receiving the same study treatment to which they have been randomly assigned for.

Actual start date of recruitment	24 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Germany: 20

Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	41
EEA total number of subjects	36

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)	36
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects were subjects who had successfully completed the TR03 study. A total of forty-one subjects were enrolled in the study. Thirty-six (87.8%) subjects were treated and of these, 16 (44.4%) subjects completed the study.

Pre-assignment

Screening details:

Subjects either entered directly into the drug treatment period (worst itch NRS ≥5) or entered an 12-weeks extended screening period of a no-drug treatment observation period (worst itch NRS <5) based on their reported NRS scores on the first visit (Visit 1a).

Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen failure: 5

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nalbuphine 90mg BID target dose

Arm description:

Nalbuphine HCl ER tablets: 90 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Arm type	Experimental
Investigational medicinal product name	Nalbuphine HCl ER
Investigational medicinal product code	
Other name	(NAL ER)
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were titrated to tolerability beginning with a 30-mg dose on Day 1 (Visit 1a or Visit 1b) with a dose increase of 30 mg BID not more often than every 3 to 4 days in order to attain steady-state plasma concentrations of Nalbuphine at each dose. Subjects were instructed to up-titrate beginning with a single 30-mg dose in the evening and then to begin dosing with an increased 30 mg BID dose the following day. Dose titrations were maintained for 3 to 4 days before further up-titration of the subject's dose was attempted. If the tolerance level became unacceptable to either the subject or the investigator, the dose was reduced incrementally until tolerance was stabilized (dose reduction by 30 mg BID if subject was at the 30-mg, 60-mg, 90-mg, or 120-mg dose level and dose reduction by 60 mg

BID if subject was at the 180-mg dose level). Subjects who did not tolerate the 180-mg BID dose level were down-titrated to the 120-mg BID dose level and maintained at that level when stabilized.

Arm title	Nalbuphine 180 mg BID target dose

Arm description:

Nalbuphine HCl ER tablets: 180 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension
study even if there were intervening missed doses.

Arm type	Experimental
Investigational medicinal product name	Nalbuphine HCl ER
Investigational medicinal product code	
Other name	(NAL ER)
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were titrated to tolerability beginning with a 30-mg dose on Day 1 (Visit 1a or Visit 1b) with a dose increase of 30 mg BID not more often than every 3 to 4 days in order to attain steady-state plasma concentrations of Nalbuphine at each dose. Subjects were instructed to up-titrate beginning with a single 30-mg dose in the evening and then to begin dosing with an increased 30 mg BID dose the following day. Dose titrations were maintained for 3 to 4 days before further up-titration of the subject's dose was attempted. If the tolerance level became unacceptable to either the subject or the investigator, the dose was reduced incrementally until tolerance was stabilized (dose reduction by 30 mg BID if subject was at the 30-mg, 60-mg, 90-mg, or 120-mg dose level and dose reduction by 60 mg BID if subject was at the 180-mg dose level). Subjects who did not tolerate the 180-mg BID dose level were down-titrated to the 120-mg BID dose level and maintained at that level when stabilized.

Arm title	Placebo

Arm description:

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized.

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

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

Dosage and administration details:

Approximately one-third of subjects were expected to enter the study after having received placebo in the TR03 study.

Number of subjects in period 1[1]	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo
Started	16	8	12
Completed	8	5	3
Not completed	8	3	9
Failure to improve criterion met	2	-	-
Physician decision	-	-	1
Adverse event, non-fatal	2	-	3
other	-	3	3
Lack of efficacy	4	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: For up to 12 extended screening weeks, subjects in the no-drug treatment observation period were allowed to transition into the drug treatment period if their worst itch NRS increased to ≥5. After 12 extended screening weeks, subjects who were not eligible for the treatment period were considered a screen failure from the study and did not enter in the baseline for study drug administration.

Baseline characteristics

Reporting groups	
Reporting group title	Nalbuphine 90mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 90 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Reporting group title	Nalbuphine 180 mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 180 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension
study even if there were intervening missed doses.

Reporting group title	Placebo

Reporting group description:

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized.

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Reporting group values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo
Number of subjects	16	8	12
Age categorical Units: Subjects			
Adults (18-64 years)	15	6	11
From 65-84 years	1	2	1
Age continuous			
Overall, the median age was 56.5 years and ranged from 23 to 75 years.			
Units: years			
median	55.5	50.5	56.4
full range (min-max)	32 to 69	24 to 69	23 to 75
Gender categorical Units: Subjects			
Female	8	2	6
Male	8	6	6

Reporting group values	Total		

Number of subjects	36		
Age categorical Units: Subjects			
Adults (18-64 years)	32		
From 65-84 years	4		
Age continuous			
Overall, the median age was 56.5 years and ranged from 23 to 75 years.			
Units: years median full range (min-max)	--		
Gender categorical Units: Subjects			
Female	16		
Male	20		

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 41 (100%) subjects were included in the all enrolled population and 36 (87.8%) subjects were included in the safety population. Safety population consisted of all enrolled subjects who received a single dose of study drug in the TR03 extension study. The safety population was used to evaluate the safety and efficacy endpoints defined for this study.

Reporting group values	Safety population		
Number of subjects	36		
Age categorical Units: Subjects			
Adults (18-64 years)	32		
From 65-84 years	4		
Age continuous			
Overall, the median age was 56.5 years and ranged from 23 to 75 years.			
Units: years median full range (min-max)	56.5 23 to 75		
Gender categorical Units: Subjects			
Female	16		
Male	20		

End points

End points reporting groups

Reporting group title	Nalbuphine 90mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 90 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Reporting group title	Nalbuphine 180 mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 180 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension
study even if there were intervening missed doses.

Reporting group title	Placebo

Reporting group description:

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized.

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 41 (100%) subjects were included in the all enrolled population and 36 (87.8%) subjects were included in the safety population. Safety population consisted of all enrolled subjects who received a single dose of study drug in the TR03 extension study. The safety population was used to evaluate the safety and efficacy endpoints defined for this study.

Primary: A description of the incidence and nature of Treatment-emergent AEs (TEAEs) during Treatment Weeks 5 to 50

End point title	A description of the incidence and nature of Treatment-emergent AEs (TEAEs) during Treatment Weeks 5 to 50[1]

End point description:

End point type	Primary

End point timeframe:

Visit 1a was the baseline for subjects directly entering the treatment period as of Visit 1a and Visit 1b was the baseline for subjects entering the treatment period after participating for up to 50 weeks.

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: As this was a safety extension study for which subjects were recruited from subjects who had completed parent Study TR03, the sample size could not be predicted. No formal sample size

calculations were performed and no inferential statistics were planned. No formal statistical analysis was performed on safety outcomes; inferences, if any, were derived through clinical review and interpretation.

End point values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	16	8	12	36
Units: number of subjects				
TEAEs with maximum severity of Grade 1	3	2	3	8
TEAEs with maximum severity of Grade 2	9	4	6	19
TEAEs with maximum severity of Grade 3	2	2	2	6
TEAEs with maximum severity of Grade 4	1	0	0	1
TEAEs with maximum severuty of Grade 5	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-Emergent Adverse Events of Special Interest

End point title	Treatment-Emergent Adverse Events of Special Interest[2]

End point description:

Treatment-Emergent Adverse Events of Special Interest
Time to onset of event was defined as: (earliest event onset date – the date of first dose of study drug + 1). For subjects who did not experience an event, time to onset was censored at the date of their last study visit. Duration of event was defined as: (event resolution date – event onset date + 1). For subjects with an event that remained ongoing at the time of study discontinuation, event duration was censored at the date of their last study visit. For some treatment administrations, time to onset of first event (days) and duration of first event (days) were not not calculable.

End point type	Primary

End point timeframe:

Visit 1a was the baseline for subjects directly entering the treatment period as of Visit 1a and Visit 1b was the baseline for subjects entering the treatment period after participating for up to 50 weeks.

Notes:

[2] - 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: As this was a safety extension study for which subjects were recruited from subjects who had completed parent Study TR03, the sample size could not be predicted. No formal sample size calculations were performed and no inferential statistics were planned. No formal statistical analysis was performed on safety outcomes; inferences, if any, were derived through clinical review and interpretation.

End point values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	16	8	12	36
Units: number of subjects experienced the TEAE				
Nausea	2	1	6	9

Vomiting	0	0	1	1
Constipation	2	1	2	5
Somnolence	1	0	3	4
Sedation	0	0	0	0
Dizziness	4	2	2	8
Vertigo	1	0	5	6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Worst Itch Intensity NRS at Visit 2/Week 3

End point title	Change From Baseline in Worst Itch Intensity NRS at Visit 2/Week 3

End point description:

Change from baseline: post-baseline value – baseline value. For the change from baseline, only subjects with a value at both baseline visit and the specific post-baseline week were included.

Numerical Rating Scale (NRS) score ranges from 0 (no itching) to 10 (worst possible Itching). Baseline was defined as the worst itch intensity NRS score at Visit 1a or 1b prior to treatment with study drug. Last observed post-baseline value was defined as the worst itch intensity NRS score at the last post-baseline visit, up to and including the washout and safety follow-up period visit. Only subjects with a value at both baseline visit and a post-baseline visit were included.

All efficacy endpoints were evaluated through the generation of descriptive summary statistics.

End point type	Secondary

End point timeframe:

From week 5 to up to 50 weeks, followed by 2-week washout for a total of 53 weeks.

End point values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	16[3]	6[4]	12[5]	34[6]
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
Visit 3/Week 5	-2.4 (± 2.3)	-1 (± 1.7)	-1.8 (± 2.2)	-2 (± 2.2)

Notes:

[3] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[4] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[5] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[6] - Only patients with a value at both baseline visit and a post-baseline visit are included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Worst Itch Intensity NRS at VISIT 14/EOT

End point title	Change From Baseline in Worst Itch Intensity NRS at VISIT 14/EOT

End point description:

Change from baseline: post-baseline value – baseline value. For the change from baseline, only subjects with a value at both baseline visit and the specific post-baseline week were included.

Numerical Rating Scale (NRS) score ranges from 0 (no itching) to 10 (worst possible Itching). Baseline was defined as the worst itch intensity NRS score at Visit 1a or 1b prior to treatment with study drug. Last observed post-baseline value was defined as the worst itch intensity NRS score at the last post-baseline visit, up to and including the washout and safety follow-up period visit. Only subjects with a value at both baseline visit and a post-baseline visit were included.

All efficacy endpoints were evaluated through the generation of descriptive summary statistics.

End point type	Secondary

End point timeframe:

From week 5 to up to 50 weeks, followed by 2-week washout for a total of 53 weeks.

End point values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8[7]	5[8]	3[9]	16[10]
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
VISIT 14/EOT	-4.6 (± 1.4)	-4.2 (± 1.1)	-3 (± 1.0)	-4.2 (± 1.3)

Notes:

[7] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[8] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[9] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[10] - Only patients with a value at both baseline visit and a post-baseline visit are included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Worst Itch Intensity NRS at VISIT 15/WASHOUT FU

End point title	Change From Baseline in Worst Itch Intensity NRS at VISIT 15/WASHOUT FU

End point description:

Change from baseline: post-baseline value – baseline value. For the change from baseline, only subjects with a value at both baseline visit and the specific post-baseline week were included.

Numerical Rating Scale (NRS) score ranges from 0 (no itching) to 10 (worst possible Itching). Baseline was defined as the worst itch intensity NRS score at Visit 1a or 1b prior to treatment with study drug. Last observed post-baseline value was defined as the worst itch intensity NRS score at the last post-baseline visit, up to and including the washout and safety follow-up period visit. Only subjects with a value at both baseline visit and a post-baseline visit were included.

All efficacy endpoints were evaluated through the generation of descriptive summary statistics.

End point type	Secondary

End point timeframe:

From week 5 to up to 50 weeks, followed by 2-week washout for a total of 53 weeks.

End point values	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo	Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8[11]	5	3[12]	15[13]
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
VISIT 15/WASHOUT FU	-3.3 (± 1.7)	-4.3 (± 1.9)	-3 (± 1.7)	-3.5 (± 1.7)

Notes:

[11] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[12] - Only patients with a value at both baseline visit and a post-baseline visit are included.

[13] - Only patients with a value at both baseline visit and a post-baseline visit are included.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assigned to a study period based on the planned study visit dates, where the planned visit date for Visit 1a/1b is the date of first dose of study drug.

Adverse event reporting additional description:

The total number of serious adverse events (SAEs) counts all treatment-emergent SAEs for subjects. At each level of subject summarization, a subject was counted once if the subject reported 1 or more events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Nalbuphine 90mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 90 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Reporting group title	Nalbuphine 180 mg BID target dose

Reporting group description:

Nalbuphine HCl ER tablets: 180 mg target dose.

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized. Subjects were only dispensed a single strength of the study drug (e.g., either 30-mg bottles or 60-mg bottles at a visit).

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Reporting group title	Placebo

Reporting group description:

Subjects enrolled into TR03 extension and received drug as early as approximately 2 weeks following their last dose of study drug in the parent TR03 study. TR03 core study patients who provided consent to participate in the TR03 extension study by the TR03 core study treatment to which they were randomized.

Completion is defined as completing study drug treatment through the End of Treatment Visit (TV14) during the TR03 extension study even if there were intervening missed doses.

Serious adverse events	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tenosynovitis stenosans			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulnocarpal abutment syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Nalbuphine 90mg BID target dose	Nalbuphine 180 mg BID target dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	8 / 8 (100.00%)	11 / 12 (91.67%)
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 16 (25.00%)	2 / 8 (25.00%)	2 / 12 (16.67%)
occurrences (all)	4	2	2
Somnolence			

subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	3 / 12 (25.00%)
occurrences (all)	1	0	3
Headache			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 16 (25.00%)	1 / 8 (12.50%)	3 / 12 (25.00%)
occurrences (all)	4	1	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	4 / 12 (33.33%)
occurrences (all)	1	0	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 16 (12.50%)	1 / 8 (12.50%)	6 / 12 (50.00%)
occurrences (all)	2	1	6
Constipation			
subjects affected / exposed	2 / 16 (12.50%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	3 / 16 (18.75%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Pruritus			

subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 8 (25.00%)	3 / 12 (25.00%)
occurrences (all)	0	2	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 16 (12.50%)	3 / 8 (37.50%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Erysipelas			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2015	Protocol Amendment 1 included the following changes: • Added failure-to-improve criteria • Added post study drug discontinuation follow-up • Added substance abuse exclusion and discontinuation criteria • Provided clarity on the concomitant use of opioids • Added limits for chronic concomitant use of anti-pruritics • Added limits to histology to select sites and presented the biopsy as an optional procedure • Added a DSMB • Added central cardiac core laboratory read of study ECGs • Added exclusion criteria related to cardiac safety, as well as protocol language • Added the SOWS • Added an additional safety assessment instrument related to neurologic exam assessment • Provided clarity in the transition of subjects from the observation period to the treatment period • Provided clarity on the titration schedule and dose adjustment processes • Included gender related PK and AE information from previous studies • Incorporated EU directives • Incorporated clarifications, administrative changes, and correction of typographical errors throughout the protocol.
02 June 2016	Protocol Amendment 2 included the following main changes: • Increased the potential number of sites globally; Clarified the timeframe for conducting Visit 1a (including obtaining informed consent) and eligibility for study participation; Added that there could be no more than 30 days between the last dose of TR03 study drug and Visit 1a; Added that abstinent female subjects of childbearing potential could participate in the study with appropriate counseling of study requirements; Added that subjects with a serum potassium levels below the lower limit of normal at TR03 Visit 5 will be excluded and that serum potassium levels below the lower limit of normal at Visit 1a should be repeated, with supplementation provided as appropriate; Clarified that subjects must not have a QTcF interval >450ms on the Visit 1a ECG; Required that a subject's heart rate be >50 bpm on all screening measurements. Any resting heart rate of <50 bpm was to be repeated once after 5 minutes in the supine position, and if it remained <50 bpm during the repeat, the subject was considered a screen failure; Clarified that the DSMB periodically review safety data during the time period that the blinded part of the nalbuphine HCl program remained ongoing, Required that urine pregnancy tests be performed on female subjects of childbearing potential, regardless of self-reported sexual and/or birth control status, at the required intervals per protocol; Implemented dosing compliance assessments and documentation at protocol required study visits; Clarified that paper versions of the PROs were to be administered for the study, including the Worst NRS, beginning at Visit 1a and continuing for all study visits, e-diary included; Added completion of the PAS at all study visits; Clarified the difference between the early termination subject (withdrawal of consent) and a subject with premature discontinuation of study drug treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported