

**Clinical trial results:****A Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCL ER Tablets in Prurigo Nodularis Patients****Summary**

EudraCT number	2013-005627-17
Trial protocol	DE PL AT
Global end of trial date	11 August 2016

**Results information**

Result version number	v1 (current)
This version publication date	29 June 2017
First version publication date	29 June 2017

**Trial information****Trial identification**

Sponsor protocol code	TR03
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174419
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, Connecticut 06510
Public contact	Clinical Trial Information, Trevi Therapeutics, Inc., +1 203304-2499, roberta.duncan@trevitherapeutics.com
Scientific contact	Clinical Trial Information, Trevi Therapeutics, Inc., +1 203304-2499, roberta.duncan@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:

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## Results analysis stage

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Analysis stage	Final
Date of interim/final analysis	11 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2016
Global end of trial reached?	Yes
Global end of trial date	11 August 2016
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

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Main objective of the trial:

The primary objectives of the study are:

- To evaluate the effects of two doses of nalbuphine HCl ER tablets on the 7-day average daily worst itch (i.e., most severe) intensity during the last 7 days of the Fixed Dose Period ("Evaluation visit"; Visit 5) compared to baseline, as measured by daily electronic patient diary records for the Numerical Rating Scale (NRS) and reported as the proportion of patients with at least a 30% reduction in the baseline 7-day average daily worst itch NRS score
  - To evaluate the safety and tolerability of nalbuphine HCl ER in the study population
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Protection of trial subjects:

Before the initiation of study-specific procedures, the patients were given a complete explanation of the purpose of the study, evaluations to be conducted, and risks/benefits for study participation. Patients were closely monitored for safety. Adverse events (AEs) were continuously evaluated throughout the study (in particular AEs of special interest: nausea, vomiting, constipation, somnolence, sedation, dizziness, and vertigo and AEs associated with abuse-potential) and vital sign measurements, locally and central cardiac core laboratory 12-lead electrocardiograms (ECGs) readings, physical examination, clinical laboratory testing, and neurological examination were conducted to monitor patient safety.

An unblinded, independent Data Safety Monitoring Board (DSMB) periodically reviewed safety data.

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Background therapy:

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.

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Evidence for comparator:

Placebo tablets, twice daily (BID)

Actual start date of recruitment	30 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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## Population of trial subjects

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### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Germany: 29

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Worldwide total number of subjects	63
EEA total number of subjects	48

Notes:

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**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)	53
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were enrolled at 4 sites in the United States, 2 sites in Germany, and 1 site each in Austria and Poland.

### Pre-assignment

Screening details:

Male or female patients aged 18 years and older, who had been suffering from PN lesions involving 2 distinct anatomical areas with mean worst itch score on numerical rating scale  $\geq 5$ .

### Period 1

Period 1 title	Titration period (1-2week)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Nalbuphine HCl ER tablets: 90 mg BID target dose
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Arm description:

Nalbuphine HCl ER tablets: 90 mg BID target dose

Arm type	Experimental
Investigational medicinal product name	Nalbuphine HCl ER tablets 90 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Nalbuphine HCl ER tablets 90 mg twice daily (BID)

<b>Arm title</b>	Nalbuphine HCl ER tablets: 180 mg BID target dose
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Arm description:

Nalbuphine HCl ER tablets: 180 mg BID target dose

Arm type	Experimental
Investigational medicinal product name	Nalbuphine HCl ER tablets 180 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Nalbuphine HCl ER tablets 180 mg twice daily (BID)

<b>Arm title</b>	Placebo tablets
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Arm description:

Placebo tablets BID.

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

Dosage and administration details:

Placebo tablet twice daily (BID),

Number of subjects in period 1	Nalbuphine HCl ER tablets: 90 mg BID target dose	Nalbuphine HCl ER tablets: 180 mg BID target dose	Placebo tablets
Started	22	19	22
Completed	22	18	22
Not completed	0	1	0
randomization error	-	1	-

## Period 2

Period 2 title	Fixed Dose Period: 8 weeks (Weeks 3 -10)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Nalbuphine HCl ER tablets: 90 mg BID target dose
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Arm description:

Nalbuphine HCl ER tablets: 90 mg BID target dose

Arm type	Experimental
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Investigational medicinal product name	Nalbuphine HCl ER tablets 90 mg
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Modified-release tablet
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Routes of administration	Oral use
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Dosage and administration details:

Nalbuphine HCl ER tablets 90 mg twice daily (BID)

<b>Arm title</b>	Nalbuphine HCl ER tablets: 180 mg BID target dose
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Arm description:

Nalbuphine HCl ER tablets: 180 mg BID target dose

Arm type	Experimental
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Investigational medicinal product name	Nalbuphine HCl ER tablets 180 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Nalbuphine HCl ER tablets 180 mg twice daily (BID)

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

Dosage and administration details:

Placebo tablets twice daily (BID).

Investigational medicinal product name	Nalbuphine HCl ER tablets 90 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Nalbuphine HCl ER tablets 90 mg twice daily (BID)

<b>Arm title</b>	Placebo tablets
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Arm description:

Placebo tablets BID.

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

Dosage and administration details:

Placebo tablet twice daily (BID),

Number of subjects in period 2	Nalbuphine HCl ER tablets: 90 mg BID target dose	Nalbuphine HCl ER tablets: 180 mg BID target dose	Placebo tablets
Started	22	18	22
Completed	18	12	20
Not completed	4	6	2
adverse events	3	5	1
Lack of efficacy	1	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Titration period (1-2week)
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Reporting group description: -

Reporting group values	Titration period (1-2week)	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
Adults (18-64 years)	53	53	
From 65-84 years	10	10	
Gender categorical Units: Subjects			
Female	35	35	
Male	28	28	

### Subject analysis sets

Subject analysis set title	The MITT analysis set
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The MITT population consisted of all randomly assigned patients who provided a baseline calculated NRS and at least 1 postbaseline NRS during randomized treatment.

Subject analysis set title	Safety Analysis Set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety population will consist of all randomized patients who have received a single dose of study medication.

Reporting group values	The MITT analysis set	Safety Analysis Set	
Number of subjects	62	62	
Age categorical Units: Subjects			
Adults (18-64 years)	52	52	
From 65-84 years	10	10	
Gender categorical Units: Subjects			
Female	34	34	
Male	28	28	

## End points

### End points reporting groups

Reporting group title	Nalbuphine HCl ER tablets: 90 mg BID target dose
Reporting group description:	Nalbuphine HCl ER tablets: 90 mg BID target dose
Reporting group title	Nalbuphine HCl ER tablets: 180 mg BID target dose
Reporting group description:	Nalbuphine HCl ER tablets: 180 mg BID target dose
Reporting group title	Placebo tablets
Reporting group description:	Placebo tablets BID.
Reporting group title	Nalbuphine HCl ER tablets: 90 mg BID target dose
Reporting group description:	Nalbuphine HCl ER tablets: 90 mg BID target dose
Reporting group title	Nalbuphine HCl ER tablets: 180 mg BID target dose
Reporting group description:	Nalbuphine HCl ER tablets: 180 mg BID target dose
Reporting group title	Placebo tablets
Reporting group description:	Placebo tablets BID.
Subject analysis set title	The MITT analysis set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	The MITT population consisted of all randomly assigned patients who provided a baseline calculated NRS and at least 1 postbaseline NRS during randomized treatment.
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	The safety population will consist of all randomized patients who have received a single dose of study medication.

### Primary: The proportion of patients with at least a 30% reduction in the 7-day average daily

End point title	The proportion of patients with at least a 30% reduction in the 7-day average daily
End point description:	At least 30% reduction in 7-day worst itch intensity NRS from baseline to week 10 Modified Intent-To-Treat Population. Patients with a 30% or greater reduction in worst itch NRS from baseline will be defined as responders. Baseline is defined as the mean of the worst itch NRS scores across the 7 days prior to the baseline visit. The week 10 worst itch intensity NRS is defined as the average of the 7 consecutive days of diary data during study week 10.
End point type	Primary
End point timeframe:	From Baseline to Week 10

<b>End point values</b>	Nalbuphine HCl ER tablets: 90 mg BID target dose	Nalbuphine HCl ER tablets: 180 mg BID target dose	Placebo tablets	The MITT analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	18	22	62
Units: number of subjects				
responders	6	9	8	23
non-responders	12	3	12	27

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Plan, Final 1.0
Comparison groups	Nalbuphine HCl ER tablets: 180 mg BID target dose v Nalbuphine HCl ER tablets: 90 mg BID target dose v Placebo tablets
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.026 <sup>[2]</sup>
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Statistical tests were two-sided evaluations comparing each nalbuphine HCl ER dose to placebo and were conducted at an overall 0.05 significance level using a "drop-down approach", unless specified otherwise.

[2] - P-value was for comparing each nalbuphine dose to placebo from a Cochran-Mantel-Haenszel test, adjusting for study site.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded starting with the signing of the first informed consent. All AEs were collected through the washout and safety follow-up visit (Visit 6) (or early termination visit).

Adverse event reporting additional description:

The safety population consists of all randomized patients who have received a single dose of study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Safety population
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Reporting group description:

The safety population consists of all randomized patients who have received a single dose of study medication. The safety population was used in all safety analyses.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 62 (4.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Safety population		
Total subjects affected by non-serious adverse events subjects affected / exposed	44 / 62 (70.97%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	158		
Headache			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	158		
Restless legs syndrome			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	158		
Somnolence			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	158		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	158		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	158		
Tinnitus			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	158		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	158		
Constipation			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	158		

Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 158		
Toothache subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 158		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158		
Vomiting subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158		
Respiratory, thoracic and mediastinal disorders Nasal dryness subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 158		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Muscle spasms subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158  2 / 62 (3.23%) 158		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 158		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 158		
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## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported