Clinical trial results:
A Randomized Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study to Evaluate the Long-term Safety of Naldemedine for the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy

Summary

EudraCT number	2013-002949-11
Trial protocol	GB DE SE BE EE PT HU AT DK ES PL
Global end of trial date	12 January 2016

Results information

Result version number	v1 (current)
This version publication date	09 April 2017
First version publication date	09 April 2017

Trial information

Trial identification

Sponsor protocol code	1326V9235

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01965652
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shionogi Inc.
Sponsor organisation address	300 Campus Drive , Florham Park, United States, NJ 07932
Public contact	Juan Camilo Arjona Ferreira, Shionogi Inc., +1 8008499407, shionogiclintrials-admin@shionogi.co.jp
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2016
Global end of trial reached?	Yes
Global end of trial date	12 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the overall safety and tolerability of naldemedine in subjects with non-malignant chronic pain receiving a stable opioid therapy regimen for ≥1 month and having opioid-induced constipation (OIC)

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time.
In order to minimize the risk for severe constipation, particularly in subjects potentially receiving placebo, the study design allowed for use of rescue laxatives (provided by the sponsor) in subjects who did not have a bowel movement for 72 hours or more, regardless of the subject being on a regular laxative regimen or not.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	United States: 1049
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 57
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 34

Worldwide total number of subjects	1246
EEA total number of subjects	161

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)	1068
From 65 to 84 years	178
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period consists of a minimum of 14 days and maximum 28-day period.

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	naldemedine 0.2 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	naldemedine 0.2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet containing 0.2 mg of the active compound was administered once daily (QD) for the 52 weeks of treatment.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet was administered once daily (QD) for the 52 weeks of treatment.

Number of subjects in period 1	naldemedine 0.2 mg	Placebo
Started	623	623
Completed	413	413
Not completed	210	210
Adverse event, serious fatal	3	4
Consent withdrawn by subject	62	69
Adverse event, non-fatal	40	37

Other	18	21
Pregnancy	-	1
Lost to follow-up	53	40
Protocol deviation	34	38

Baseline characteristics

Reporting groups	
Reporting group title	naldemedine 0.2 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	naldemedine 0.2 mg	Placebo	Total
Number of subjects	623	623	1246
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	521	547	1068
From 65-84 years	102	76	178
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.4	52.7	
standard deviation	± 11.69	± 10.53	-
Gender categorical Units: Subjects			
Female	385	404	789
Male	238	219	457

End points

End points reporting groups

Reporting group title	naldemedine 0.2 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Assessments of summary measures of treatment-emergent adverse events (TEAEs)

End point title	Assessments of summary measures of treatment-emergent adverse events (TEAEs)
End point description:	

End point type	Primary
End point timeframe:	
From Baseline to week 52	

End point values	naldemedine 0.2 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	621	619		
Units: Percentage of frequency of TEAEs				
number (not applicable)	68.4	72.1		

Statistical analyses

Statistical analysis title	Assessments of summary measures of TEAEs
Comparison groups	Placebo v naldemedine 0.2 mg
Number of subjects included in analysis	1240
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of proportion
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	1.5

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Between the first dose and 14 days after the last dose of study drug	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	naldemedine 0.2 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	naldemedine 0.2 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 621 (9.66%)	73 / 619 (11.79%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung adenocarcinoma			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			

subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 621 (0.16%)	3 / 619 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 621 (0.32%)	3 / 619 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 621 (0.32%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium increased			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 621 (0.32%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery restenosis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			

subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 621 (0.32%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 621 (0.00%)	2 / 619 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac failure congestive			
subjects affected / exposed	1 / 621 (0.16%)	2 / 619 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal claudication			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	2 / 621 (0.32%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 621 (0.32%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric volvulus			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder prolapse			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephrolithiasis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 621 (0.32%)	5 / 619 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc degeneration			
subjects affected / exposed	0 / 621 (0.00%)	2 / 619 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 621 (0.32%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 621 (0.32%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 621 (0.81%)	3 / 619 (0.48%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			

subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 621 (0.32%)	2 / 619 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			

subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 621 (0.16%)	2 / 619 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site infection			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			

subjects affected / exposed	1 / 621 (0.16%)	0 / 619 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 621 (1.13%)	4 / 619 (0.65%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 621 (0.16%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 621 (0.00%)	1 / 619 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	naldemedine 0.2 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	419 / 621 (67.47%)	436 / 619 (70.44%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 621 (1.61%)	14 / 619 (2.26%)	
occurrences (all)	10	14	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 621 (2.09%)	10 / 619 (1.62%)	
occurrences (all)	13	11	
Headache			
subjects affected / exposed	28 / 621 (4.51%)	33 / 619 (5.33%)	
occurrences (all)	31	34	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	15 / 621 (2.42%)	12 / 619 (1.94%)	
occurrences (all)	18	12	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	14 / 621 (2.25%)	12 / 619 (1.94%)	
occurrences (all)	15	13	
Abdominal pain			
subjects affected / exposed	50 / 621 (8.05%)	18 / 619 (2.91%)	
occurrences (all)	55	19	
Abdominal pain upper			
subjects affected / exposed	30 / 621 (4.83%)	18 / 619 (2.91%)	
occurrences (all)	34	21	
Constipation			
subjects affected / exposed	19 / 621 (3.06%)	20 / 619 (3.23%)	
occurrences (all)	21	22	
Diarrhoea			
subjects affected / exposed	68 / 621 (10.95%)	33 / 619 (5.33%)	
occurrences (all)	77	42	
Flatulence			
subjects affected / exposed	11 / 621 (1.77%)	16 / 619 (2.58%)	
occurrences (all)	11	16	
Nausea			
subjects affected / exposed	49 / 621 (7.89%)	35 / 619 (5.65%)	
occurrences (all)	52	46	
Vomiting			
subjects affected / exposed	36 / 621 (5.80%)	18 / 619 (2.91%)	
occurrences (all)	40	22	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	15 / 621 (2.42%)	6 / 619 (0.97%)	
occurrences (all)	16	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	13 / 621 (2.09%)	13 / 619 (2.10%)	
occurrences (all)	13	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 621 (4.51%)	23 / 619 (3.72%)	
occurrences (all)	31	26	

Back pain			
subjects affected / exposed	34 / 621 (5.48%)	27 / 619 (4.36%)	
occurrences (all)	40	32	
Muscle spasms			
subjects affected / exposed	10 / 621 (1.61%)	16 / 619 (2.58%)	
occurrences (all)	11	16	
Pain in extremity			
subjects affected / exposed	13 / 621 (2.09%)	17 / 619 (2.75%)	
occurrences (all)	18	22	
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 621 (3.38%)	16 / 619 (2.58%)	
occurrences (all)	23	20	
Gastroenteritis viral			
subjects affected / exposed	14 / 621 (2.25%)	12 / 619 (1.94%)	
occurrences (all)	16	12	
Influenza			
subjects affected / exposed	15 / 621 (2.42%)	13 / 619 (2.10%)	
occurrences (all)	15	14	
Nasopharyngitis			
subjects affected / exposed	26 / 621 (4.19%)	29 / 619 (4.68%)	
occurrences (all)	31	33	
Sinusitis			
subjects affected / exposed	23 / 621 (3.70%)	24 / 619 (3.88%)	
occurrences (all)	26	26	
Upper respiratory tract infection			
subjects affected / exposed	36 / 621 (5.80%)	33 / 619 (5.33%)	
occurrences (all)	42	42	
Urinary tract infection			
subjects affected / exposed	38 / 621 (6.12%)	51 / 619 (8.24%)	
occurrences (all)	44	59	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2013	• Added a serum pregnancy test at Visit 2 (Day 1) prior to dosing for all females of childbearing potential • Added directions for collecting data for laxative use during the Treatment Period at study site visits and recording the data on the CRF • Added directions for recording all opioid pain medication(s) dosing daily in the eDiary during the Screening Period and for the first 2 weeks of the Treatment Period • Added directions that opioid therapy was then to be captured on the CRF throughout the entire duration of the study • Added list of prohibited medications that were not to be taken by subjects at any time during the study; specified that the Visit 8 (Week 24) safety data would be analyzed by the DSMB
16 June 2014	• Added text to the synopsis and inclusion criteria stating that subjects must meet the following criteria based on an eDiary to be completed over a 14-consecutive-day qualifying period during the 28-day Screening Period: no more than 4 SBMs total over the 14-consecutive-day qualifying period. In addition, no more than 3 SBMs in a given week of the qualifying period. • Added text to specify that subjects might use laxatives during the Screening Period. • Added text to specify that tramadol and tapentadol would not be used in the calculations for either inclusion criterion No. 3, calculation of the stable opioid regimen at a total average daily dose of ≥ 30 mg equivalents of oral morphine sulfate, or for stratification by average daily dose of 30 to 100 mg equivalents of oral morphine sulfate versus > 100 mg equivalents of oral morphine sulfate. Specified that use of tramadol and tapentadol was allowed in the trial but only in conjunction with other opioid agonists • Added subheading stating that the change in frequency of BMs from baseline to selected timepoints in the Treatment Period was to be assessed as an efficacy endpoint. Subjects were to monitor BMs during the 52-week Treatment Period and were to be asked to complete the Bowel Habits paper diary. Also that during the Treatment Period, subjects were to record BM data on the paper diary during the week prior to each of the selected study visits (ie, Bowel Habits paper diary should have been filled out during Weeks 11, 23, 35, and 51, corresponding to the week prior to Study Visits 6, 8, 10 and 13, respectively).

26 February 2015	• Change wording primary objective to "Assess the overall safety and tolerability of naldemedine in subjects with non-malignant chronic pain receiving a stable opioid therapy regimen for ≥ 1 month and having OIC." • Change sample size per alignment with ICHE1. • Modifications made to Overall Study Design and Plan: separation of Treatment Period into Core Period Data Set and Supplemental Period Data Set (Study visits and Schedule of Events remained as presented). • Precisions made regarding blinding and unblinding. • (Efficacy) Assessments changed to Secondary (Efficacy) Assessments. • Early Termination changed: subjects who terminated early should also have Follow-up Period Visit, 2 weeks after last dose of study drug. • Addition made to General Considerations: "The Core Period Data Set will consist of all subjects with at least 24 weeks of treatment (up to and including Visit 8 at minimum). The Core Period Data Set is considered a complete and "stand alone" data set that will be used for Global Registration purposes. The Supplemental Period Data Set will consist of all remaining data (study visits not completed at the time of the Core Period data lock). For Statistical purposes, a Combined data set will also be compiled that will consist of the Core Period and the Supplemental Period." • Primary endpoint changed from number of MACEs during 52-week Treatment Period to "Safety: The incidence of TEAEs, serious TEAEs, and AEs leading to discontinuation". TEAEs will be used for safety analyses. The definition of TEAE is an AE which occurs from first dose of study drug until 14 days after last study dose." • Addition AEs of Special Interest: MACEs and Assessment of Opioid Withdrawal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported