Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Naldemedine in the Treatment of Opioid-induced Constipation in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy

Summary

EudraCT number	2013-002948-91
Trial protocol	DE CZ AT ES PL
Global end of trial date	09 June 2015

Results information

Result version number	v1 (current)
This version publication date	25 June 2016
First version publication date	25 June 2016

Trial information

Trial identification

Sponsor protocol code	1315V9232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01993940
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	16 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2015
Global end of trial reached?	Yes
Global end of trial date	09 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of naldemedine compared to placebo without concomitant laxative treatment in subjects with non-malignant chronic pain receiving a stable opioid 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 rational 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 sever constipation particularly in subjects potentially receiving placebo, the study design allowed for use of laxatives in subjects who did not have a bowel movement for 72 hours or more.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 480
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	550
EEA total number of subjects	70

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)	468
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period consisted of a minimum of 2-week and maximum 4-week period. Eligibility criteria were reviewed and qualified subjects providing informed consent entered the study.

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 0.2mg

Arm description: -

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

Dosage and administration details:

One tablet containing 0.2mg of the active compound was administered once daily (QD) for the 12 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 was administered once daily (QD) for the 12 weeks of treatment

Number of subjects in period 1	naldemedine 0.2mg	Placebo
Started	276	274
Completed	237	231
Not completed	39	43
Adverse event, serious fatal	1	-
Consent withdrawn by subject	15	19

Adverse event, non-fatal	16	11
Other	1	1
Lost to follow-up	2	5
Protocol deviation	4	7

Baseline characteristics

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

Reporting group values	naldemedine 0.2mg	Placebo	Total
Number of subjects	276	274	550
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)	232	236	468
From 65-84 years	44	38	82
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.1	52.9	
standard deviation	± 10.48	± 11.4	-
Gender categorical Units: Subjects			
Female	165	168	333
Male	111	106	217

End points

End points reporting groups

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

Primary: Proportion of responders, where a responder was defined as having ≥ 9 positive-response weeks out of the 12-week treatment period and 3 positive-response weeks out of the last 4 weeks of the 12-week treatment period.

End point title	Proportion of responders, where a responder was defined as having ≥ 9 positive-response weeks out of the 12-week treatment period and 3 positive-response weeks out of the last 4 weeks of the 12-week treatment period.
End point description:	
End point type	Primary
End point timeframe:	
From Baseline to week 12	

End point values	naldemedine 0.2mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	274		
Units: Proportion of responders				
number (confidence interval 95%)				
Proportion of responders	52.5 (46.5 to 58.6)	33.6 (28 to 39.5)		

Statistical analyses

Statistical analysis title	Proportion of Responders
Comparison groups	naldemedine 0.2mg v Placebo
Number of subjects included in analysis	550
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion difference
Point estimate	18.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.8
upper limit	27
Variability estimate	Standard error of the mean
Dispersion value	4.12

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Between the first dose and 28 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 0.2mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	naldemedine 0.2mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 271 (3.32%)	13 / 274 (4.74%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 271 (0.37%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Mental status changes			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			

subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 271 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (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			
Renal failure acute			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 271 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (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	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	naldemedine 0.2mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 271 (49.45%)	127 / 274 (46.35%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 271 (2.21%)	0 / 274 (0.00%)	
occurrences (all)	6	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 271 (2.21%)	3 / 274 (1.09%)	
occurrences (all)	21	9	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	6 / 271 (2.21%)	0 / 274 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 271 (5.17%)	3 / 274 (1.09%)	
occurrences (all)	19	4	
Diarrhoea			
subjects affected / exposed	24 / 271 (8.86%)	5 / 274 (1.82%)	
occurrences (all)	26	5	
Flatulence			
subjects affected / exposed	6 / 271 (2.21%)	9 / 274 (3.28%)	
occurrences (all)	7	9	
Nausea			
subjects affected / exposed	13 / 271 (4.80%)	9 / 274 (3.28%)	
occurrences (all)	15	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 271 (2.21%)	2 / 274 (0.73%)	
occurrences (all)	6	2	
Back pain			
subjects affected / exposed	10 / 271 (3.69%)	6 / 274 (2.19%)	
occurrences (all)	10	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 271 (2.21%)	7 / 274 (2.55%)	
occurrences (all)	7	7	
Sinusitis			
subjects affected / exposed	4 / 271 (1.48%)	7 / 274 (2.55%)	
occurrences (all)	4	7	
Upper respiratory tract infection			
subjects affected / exposed	7 / 271 (2.58%)	5 / 274 (1.82%)	
occurrences (all)	9	5	
Urinary tract infection			
subjects affected / exposed	5 / 271 (1.85%)	14 / 274 (5.11%)	
occurrences (all)	5	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2014	The key changes that Amendment 1 (11 June 2014) made to the protocol included the following: added clarification of discontinuing regular use of laxatives at start of screening and through the 12-week Treatment Period, clarification of stratification based on morphine-equivalent dosing as well as redefined allowable use of tramadol and tapentadol, clarification of exclusion criteria related to severe constipation prior to and during the Screening Period, and clarification of primary efficacy endpoint related to last observation carried forward (LOCF).
16 October 2014	The key changes that Amendment 2 (16 October 2014) made to the protocol included the following: revised secondary efficacy endpoints to provide a more thorough clinical efficacy summary of naldemedine including effects from baseline to endpoint, baseline to the first week, straining, and CSBMs; added an exploratory endpoint to further assess the effect on SBMs without straining over time; removed PK assessment as an exploratory endpoint; changed the mITT Population to produce a population that more accurately accounted for the challenges encountered by subjects required to use an EDC tool; modified the Safety Population to be more inclusive in order to obtain a larger population; and further clarified the definition of insufficient primary endpoint data and "nonresponse" week.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported