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	2013-002241-11
Trial protocol	DE AT CZ GB ES PL
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	21 July 2016

Trial information

Trial identification

Sponsor protocol code	1314V9231

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01965158
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	10 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2015
Global end of trial reached?	Yes
Global end of trial date	22 January 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 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 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	29 August 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	Poland: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	United States: 459
Worldwide total number of subjects	545
EEA total number of subjects	86

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)	459
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period consists 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 0.2 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 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 tablet was administered once daily (QD) for the 12 weeks of treatment.

Number of subjects in period 1	naldemedine 0.2 mg	Placebo
Started	273	272
Completed	233	238
Not completed	40	34
Consent withdrawn by subject	16	23
Other	2	-

Adverse event	14	5
Lost to follow-up	7	5
Protocol deviation	1	1

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	273	272	545
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)	234	225	459
From 65-84 years	39	47	86
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.3	53.4	
standard deviation	± 10.44	± 11.03	-
Gender categorical Units: Subjects			
Female	161	168	329
Male	112	104	216

End points

End points reporting groups

Reporting group title	naldemedine 0.2 mg
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 0.2 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	272		
Units: Percentage				
number (confidence interval 95%)				
Proportion of Responders	47.6 (41.6 to 53.7)	34.6 (28.9 to 40.5)		

Statistical analyses

Statistical analysis title	Proportion of Responders
Comparison groups	Placebo v naldemedine 0.2 mg
Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion difference
Point estimate	13

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	21.3
Variability estimate	Standard error of the mean
Dispersion value	4.19

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 0.2 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	14 / 271 (5.17%)	5 / 272 (1.84%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (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	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Patent ductus arteriosus			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (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			
Transient ischaemic attack			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (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 failure			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (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 / 271 (0.37%)	0 / 272 (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 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 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 0.2 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 271 (46.86%)	122 / 272 (44.85%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 271 (1.48%)	7 / 272 (2.57%)	
occurrences (all)	4	7	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 271 (2.21%)	3 / 272 (1.10%)	
occurrences (all)	7	8	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 271 (5.90%)	5 / 272 (1.84%)	
occurrences (all)	17	6	
Abdominal pain upper			
subjects affected / exposed	6 / 271 (2.21%)	2 / 272 (0.74%)	
occurrences (all)	6	2	
Diarrhoea			
subjects affected / exposed	18 / 271 (6.64%)	8 / 272 (2.94%)	
occurrences (all)	18	8	
Nausea			
subjects affected / exposed	13 / 271 (4.80%)	7 / 272 (2.57%)	
occurrences (all)	13	7	
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	6 / 271 (2.21%)	2 / 272 (0.74%)	
occurrences (all)	6	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 271 (1.85%)	9 / 272 (3.31%)	
occurrences (all)	5	9	
Infections and infestations			
Sinusitis			
subjects affected / exposed	4 / 271 (1.48%)	6 / 272 (2.21%)	
occurrences (all)	4	7	
Upper respiratory tract infection			
subjects affected / exposed	6 / 271 (2.21%)	7 / 272 (2.57%)	
occurrences (all)	6	7	
Urinary tract infection			
subjects affected / exposed	7 / 271 (2.58%)	8 / 272 (2.94%)	
occurrences (all)	7	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2013	The key changes that Amendment 1 (4 October 2013) made to the protocol included the following: added clarification of BMCA inclusion criteria; added text to clarify eligibility criteria based on SBMs; changed text to clarify the steps taken for rescue laxative therapy; and added text to allow for Investigator discretion on medication that may have had a significant impact on the GI system or bowel habits.
11 June 2014	The key changes that Amendment 2 (11 June 2014) made to the protocol included the following: clarification of allowed laxatives during the Follow-up Period; redefined allowable use of tramadol and tapentadol for clarity; and revised time points for primary efficacy endpoint for more robust analysis.
16 October 2014	The key changes that Amendment 3 (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 definition of the mITT Population to produce a population that more accurately accounted for challenges encountered by subjects required to use an electronic data capture 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 a "non-response" week.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported