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 Hemodialysis Patients with Uremic Pruritis

Summary

EudraCT number	2013-005625-22
Trial protocol	PL RO
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	TR02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02143648
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., 001 203304-2499, Thomas.Sciascia@trevitherapeutics.com
Scientific contact	Clinical Trial Information, Trevi Therapeutics, Inc., 001 203304-2499, Thomas.Sciascia@trevitherapeutics.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

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 change from baseline in the worst itch Numerical Rating Scale (NRS) in hemodialysis patients with moderate to severe uremic pruritus.
• To evaluate the safety and tolerability of nalbuphine HCl ER in the study population.

Protection of trial subjects:

An unblinded, independent Data and Safety Monitoring Board (DSMB) reviewed safety data. The DSMB periodically reviewed group-unblinded study information (on a treatment group level, using random letters instead of actual treatments) during the conduct of the study. If necessary, unblinding of individual subject data and treatment groups was possible.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2014
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	United States: 302
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Romania: 49
Worldwide total number of subjects	373
EEA total number of subjects	71

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)	284
From 65 to 84 years	87
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 597 patients were screened of which 373 patients were randomized: 128 to nalbuphine HCl ER 60 mg BID, 120 to nalbuphine HCl ER 120 mg BID, and 125 to placebo. The safety population consisted of 369 treated patients who received at least one dose of randomized treatment.

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	Investigator, Subject

Blinding implementation details:

The study staff, patients, and Sponsor were blinded to treatment assignment to avoid potential bias. An unblinded, independent Data Safety Monitoring Board (DSMB) periodically reviewed safety data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nalbuphine 60 mg

Arm description:

Blinded titration over 2 weeks to a target dose of 60 mg twice daily (BID) followed by 6 weeks at 60 mg BID.
128 patients were randomized to nalbuphine HCl ER 60 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID patients completed the full term of study participation through the end of the post- treatment washout.

Arm type	Experimental
Investigational medicinal product name	nalbuphine hydrochloride (HCl) extended-release (ER) tablets
Investigational medicinal product code	Nalbuphine HCl ER
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

60mg BID, Oral use

Arm title	Nalbuphine 120 mg

Arm description:

Blinded titration over 2 weeks to a target dose of 120 mg BID followed by 6 weeks at 120 mg BID.
120 patients were randomized to nalbuphine HCl ER 120 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 78 (65.0%) nalbuphine HCl ER 120 mg BID patients completed the full term of study participation through the end of the post- treatment washout.

Arm type	Experimental
Investigational medicinal product name	nalbuphine hydrochloride (HCl) extended-release (ER) tablets
Investigational medicinal product code	Nalbuphine HCl ER
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

120mg BID, Oral use

Arm title	Placebo

Arm description:

Placebo x 8 weeks twice daily (BID).
125 paients were rendomized to placebo. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 101 (80.8%) placebo patients completed the full term of study participation through the end of the post- treatment washout.

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:

Treatment was administered as oral tablets BID without regard to food. An equal number of tablets was administered to the active treatment and placebo arm for all given treatment visits over the duration of the study.

Number of subjects in period 1	Nalbuphine 60 mg	Nalbuphine 120 mg	Placebo
Started	128	120	125
Completed	74	78	101
Not completed	54	42	24
Consent withdrawn by subject	11	9	5
Adverse event, non-fatal	33	27	7
patient's non-compliance with protocol	3	3	4
Other	3	2	4
Death	-	-	1
Renal transplantation	1	1	1
Patient transferred from dialysis unit	1	-	1
Lost to follow-up	1	-	-
Lack of efficacy	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Nalbuphine 60 mg
Reporting group description:	
Blinded titration over 2 weeks to a target dose of 60 mg twice daily (BID) followed by 6 weeks at 60 mg BID. 128 patients were randomized to nalbuphine HCl ER 60 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID patients completed the full term of study participation through the end of the post- treatment washout.	
Reporting group title	Nalbuphine 120 mg
Reporting group description:	
Blinded titration over 2 weeks to a target dose of 120 mg BID followed by 6 weeks at 120 mg BID. 120 patients were randomized to nalbuphine HCl ER 120 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 78 (65.0%) nalbuphine HCl ER 120 mg BID patients completed the full term of study participation through the end of the post- treatment washout.	
Reporting group title	Placebo
Reporting group description:	
Placebo x 8 weeks twice daily (BID). 125 paients were rendomized to placebo. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 101 (80.8%) placebo patients completed the full term of study participation through the end of the post- treatment washout.	

Reporting group values	Nalbuphine 60 mg	Nalbuphine 120 mg	Placebo
Number of subjects	128	120	125
Age categorical Units: Subjects			
Adults (18-64 years)	100	90	94
From 65-84 years	27	30	30
85 years and over	1	0	1
Age continuous Units: years			
median	56.5	55	56
standard deviation	± 12	± 12.2	± 13
Gender categorical Units: Subjects			
Male	70	69	74
Female	58	51	51

Reporting group values	Total		
Number of subjects	373		
Age categorical Units: Subjects			
Adults (18-64 years)	284		
From 65-84 years	87		
85 years and over	2		
Age continuous Units: years			
median			
standard deviation	-		

Gender categorical Units: Subjects			
Male	213		
Female	160		

Subject analysis sets

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID, 78 (65.0%) nalbuphine HCl ER 120 mg BID, and 101 (80.8%) placebo patients completed the full term of study participation through the end of the post-treatment washout.

Subject analysis set title	Modified-Intent-to-Treat (MITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) analysis included all but two randomized patients, both excluded because they did not have any post-baseline evaluation.
The demographic and baseline characteristics for the MITT population were similar to those of the safety population.
Modified intent-to-treat population consisted of: Nalbuphine 60 mg: 128; Nalbuphine 120 mg: 120; Placebo: 123.

Reporting group values	Safety	Modified-Intent-to-Treat (MITT)	
Number of subjects	369	371	
Age categorical Units: Subjects			
Adults (18-64 years)	282	282	
From 65-84 years	85	87	
85 years and over	2	2	
Age continuous Units: years			
median	56	56	
standard deviation	± 12.4	± 12.4	
Gender categorical Units: Subjects			
Male	211	212	
Female	158	159	

End points

End points reporting groups

Reporting group title	Nalbuphine 60 mg

Reporting group description:

Blinded titration over 2 weeks to a target dose of 60 mg twice daily (BID) followed by 6 weeks at 60 mg BID.
128 patients were randomized to nalbuphine HCl ER 60 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID patients completed the full term of study participation through the end of the post- treatment washout.

Reporting group title	Nalbuphine 120 mg

Reporting group description:

Blinded titration over 2 weeks to a target dose of 120 mg BID followed by 6 weeks at 120 mg BID.
120 patients were randomized to nalbuphine HCl ER 120 mg BID. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 78 (65.0%) nalbuphine HCl ER 120 mg BID patients completed the full term of study participation through the end of the post- treatment washout.

Reporting group title	Placebo

Reporting group description:

Placebo x 8 weeks twice daily (BID).
125 paients were rendomized to placebo. The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 101 (80.8%) placebo patients completed the full term of study participation through the end of the post- treatment washout.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID, 78 (65.0%) nalbuphine HCl ER 120 mg BID, and 101 (80.8%) placebo patients completed the full term of study participation through the end of the post-treatment washout.

Subject analysis set title	Modified-Intent-to-Treat (MITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified-Intent-to-Treat (MITT) analysis included all but two randomized patients, both excluded because they did not have any post-baseline evaluation.
The demographic and baseline characteristics for the MITT population were similar to those of the safety population.
Modified intent-to-treat population consisted of: Nalbuphine 60 mg: 128; Nalbuphine 120 mg: 120; Placebo: 123.

Primary: Mean Reduction in Worst itch NRS During the Evaluation Period (MITT Population)

End point title	Mean Reduction in Worst itch NRS During the Evaluation Period (MITT Population)[1]

End point description:

Primary TR02 outcome variable: change from baseline value to the Evaluation Period value (Weeks 7 and 8) in a patient's mean Worst Itch NRS for each dose of nalbuphine, separately, and placebo.
Statistical significance for the comparison of each nalbuphine arm to placebo was defined as a two-sided p-value ≤ 0.05.
A statistically significant reduction compared to placebo in Worst Itch NRS was demonstrated for the nalbuphine 120 mg BID (p=0.017) (Table 1).

End point type	Primary

End point timeframe:

Change from baseline value to the Evaluation Period value (Weeks 7 and 8).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please refer to the attached table - Table 1: TR02 Mean Reduction in Worst itch NRS During the Evaluation Period (MITT Population)

End point values	Modified-Intent-to-Treat (MITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	274			
Units: itch NRS				
arithmetic mean (standard deviation)	-3.1 (± 2.3)			

Attachments (see zip file)	Table 1/Table 1.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: Mean Reduction in Worst Itch NRS during the Evaluation Period Patients with Severe UP (NRS≥7) (MITT Population)

End point title	Mean Reduction in Worst Itch NRS during the Evaluation Period Patients with Severe UP (NRS≥7) (MITT Population)

End point description:

An additional analysis for the subgroup of patients with severe uremic pruritus (Worst Itch NRS ≥7) at baseline was undertaken. As can be seen in Table 2, a statistically significant mean reduction in Worst Itch NRS was demonstrated for nalbuphine HCl ER 120 mg BID compared with placebo (p=0.007); the mean (SD) reduction was -4.48 (2.50) points and the least square mean difference from placebo was -1.39 points. Mean reduction for nalbuphine HCl ER tablets 60 mg BID with severe UP was not significantly greater than for placebo, and did not meet the criteria for being clinically meaningful.

End point type	Post-hoc

End point timeframe:

Change from baseline value to the Evaluation Period value (Weeks 7 and 8).

End point values	Modified-Intent-to-Treat (MITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	137			
Units: inch NRS				
arithmetic mean (standard deviation)	-3.7 (± 2.6)			

Attachments (see zip file)	Table 2/Table 2.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At least one Treatment Emergent Adverse Event (TEAE) was reported by 94/317 (74.6%) patients in the nalbuphine 60 mg BID arm, 88/264 (73.3%) patients in the nalbuphine 120 mg BID arm, and 75/195 (61.0%) patients in the placebo arm of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	safety population

Reporting group description:

The safety population consisted of 369 treated patients who received at least one (AM or PM) dose of randomized treatment. A total of 74 (57.5%) nalbuphine HCl ER 60 mg BID, 78 (65.0%) nalbuphine HCl ER 120 mg BID, and 101 (80.8%) placebo patients completed the full term of study participation through the end of the post-treatment washout. There were no notable differences in demographics and baseline characteristics in patients across treatment groups. The demographic and baseline characteristics for the MITT population were similar to those of the safety population.
One death occurred in Study TR02. A subject in the placebo group died following nephrectomy (performed for pyelonephritis) with the post-operative development of an abscess and sepsis.

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 369 (11.65%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions			
Local swelling			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Conversion disorder			

subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal arteriovenous malformation			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	5 / 369 (1.36%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	2 / 369 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Transient ischaemic attack				

subjects affected / exposed	2 / 369 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 369 (0.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 369 (1.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 369 (1.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Dyspepsia			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Streptococcal bacteraemia			

subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 369 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 369 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 369 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Hyperkalaemia				
subjects affected / exposed	3 / 369 (0.81%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Fluid overload				

subjects affected / exposed	4 / 369 (1.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 369 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 369 (68.29%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 369 (5.96%)		
occurrences (all)	25		
Somnolence			
subjects affected / exposed	37 / 369 (10.03%)		
occurrences (all)	43		
Gastrointestinal disorders			
Constipation	Additional description: The total number of AEs counts all treatment-emergent AEs for patients. At each level of patient summarization, a patient is counted once if the patient reported one or more events.		
subjects affected / exposed	16 / 369 (4.34%)		
occurrences (all)	16		
Diarrhoea			
subjects affected / exposed	24 / 369 (6.50%)		
occurrences (all)	27		
Nausea			
subjects affected / exposed	82 / 369 (22.22%)		
occurrences (all)	91		
Vomiting			
subjects affected / exposed	71 / 369 (19.24%)		
occurrences (all)	86		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2014	Clinical research Protocol TR02 v5.0 was produced for the following purposes: • To incorporate a Data and Safety Monitoring Board (DSMB) • To acknowledge hemodialysis adequacy guidelines • To incorporate clarifications, administrative changes and correction of typographical errors throughout the protocol. Previous version of the Protocol (version no. 4.0 of 24 June 2014) was submitted in Romania within initial submission.
10 October 2014	Clinical research Protocol TR02 v6.0 was produced for the following purposes: • To clarify the timing and window of visits during the Washout and Safety Follow-up Period related to the last dose of drug • To clarify the time period to calculate the total dose of erythropoiesis stimulating agent (ESA) • To clarify the lower end of the study drug dosing window. Protocol version no. 6.0 of 10 October 2014 was submitted in Poland within initial submission.
20 January 2015	Clinical research Protocol TR02 v7.0 was produced for the following purposes: • To add central cardiac core laboratory read of study ECGs • To incorporate EU directives • To incorporate clarifications, administrative changes and correction of typographical errors throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported