



Clinical trial results:

An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCL ER Tablets in Hemodialysis Patients with Uremic Pruritus

Summary

EudraCT number	2013-005626-29
Trial protocol	PL RO
Global end of trial date	24 November 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	TR02ext
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02143973
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trevi Therapeutics, Inc.
Sponsor organisation address	195 Church Street, 14th Floor, New Haven, Connecticut, United States, 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	23 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to evaluate the safety and tolerability of nalbuphine HCl ER tablets during a drug treatment period of up to 24 weeks.

The secondary objectives were to evaluate the safety of nalbuphine HCl ER tablets by achieved dose at the end of Treatment Period Week 3.

The exploratory objectives are to evaluate the effect of nalbuphine HCl ER tablets on:

- changes in Patient-Reported Outcome measures (NRS, Skindex-10, Itch MOS Sleep, HADS, PADS) during the Treatment Period
- percentage of patients utilizing various doses of nalbuphine HCl ER tablets by Study Week
- change in worst itch NRS and other PROs following a +/- 30 mg BID titration
- frequency and reasons for dose up- and down-titration and treatment discontinuation during the study
- changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets
- time to first use of rescue medications and the number of days of use of rescue medications for itching.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 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	Poland: 7
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	United States: 145
Worldwide total number of subjects	167
EEA total number of subjects	22

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)	140
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients who had successfully completed the TR02 study and wished to participate in TR02ext were enrolled, treated, and analyzed.

Pre-assignment

Screening details:

Of the three hundred seventy-three patients that were randomized to TR02, 184 subjects both completed TR02 and enrolled into TR02ext. 167 subjects who enrolled into TR02ext were exposed to nalbuphine HCl ER tablet administration and are the basis of the study safety population analysis.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Safety Population
-----------	-------------------

Arm description:

The nalbuphine dose was titrated based on NRS scores between Treatment Visits 1 and 3, after which time the dose achieved (30 mg QD – 120 mg BID) as of the end of Treatment Week 3 was maintained up to an additional 21 weeks.

At the end of the titration period at week 3 of the Treatment Period the distribution of dosing was 14 subjects (8.4%) at 30 mg BID, 35 subjects (21%) at 60 mg BID, 30 subjects (18%) at 90 mg BID and 70 subjects (41.9%) at 120 mg BID. 8 subjects (4.8%) were missing data. Analyzing the distribution of study drug use over the course of the study shows that 120 mg BID was the most frequent dose used by patients followed by the 60 BID dose.

Arm type	Treatment
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:

30 mg QD – 120 mg BID, Oral use

Number of subjects in period 1	Safety Population
Started	167
Completed	101
Not completed	66
Consent withdrawn by subject	18
Adverse event, non-fatal	19
Death	4
Other	15
Pregnancy	1
Renal transplantation	3

patients non-compliance with protocol	5
Lack of efficacy	1

Period 2

Period 2 title	Observation Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	No drug treatment
------------------	-------------------

Arm description:

While patients remained in the Observation Period, they were not considered enrolled into the study, but as participating in an extended screening process until they were eligible for treatment.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	No drug treatment
Started	101
Completed	101

Period 3

Period 3 title	Washout and Safety Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	No treatment
------------------	--------------

Arm description: -

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	No treatment
Started	101
Completed	101

Baseline characteristics

Reporting groups

Reporting group title	Safety Population
-----------------------	-------------------

Reporting group description:

The nalbuphine dose was titrated based on NRS scores between Treatment Visits 1 and 3, after which time the dose achieved (30 mg QD – 120 mg BID) as of the end of Treatment Week 3 was maintained up to an additional 21 weeks.

At the end of the titration period at week 3 of the Treatment Period the distribution of dosing was 14 subjects (8.4%) at 30 mg BID, 35 subjects (21%) at 60 mg BID, 30 subjects (18%) at 90 mg BID and 70 subjects (41.9%) at 120 mg BID. 8 subjects (4.8%) were missing data. Analyzing the distribution of study drug use over the course of the study shows that 120 mg BID was the most frequent dose used by patients followed by the 60 BID dose.

Reporting group values	Safety Population	Total	
Number of subjects	167	167	
Age categorical			
Units: Subjects			
Adults (18-64 years)	140	140	
From 65-84 years	27	27	
Age continuous			
Units: years			
median	53		
standard deviation	± 12.2	-	
Gender categorical			
Units: Subjects			
Female	92	92	
Male	75	75	

End points

End points reporting groups

Reporting group title	Safety Population
-----------------------	-------------------

Reporting group description:

The nalbuphine dose was titrated based on NRS scores between Treatment Visits 1 and 3, after which time the dose achieved (30 mg QD – 120 mg BID) as of the end of Treatment Week 3 was maintained up to an additional 21 weeks.

At the end of the titration period at week 3 of the Treatment Period the distribution of dosing was 14 subjects (8.4%) at 30 mg BID, 35 subjects (21%) at 60 mg BID, 30 subjects (18%) at 90 mg BID and 70 subjects (41.9%) at 120 mg BID. 8 subjects (4.8%) were missing data. Analyzing the distribution of study drug use over the course of the study shows that 120 mg BID was the most frequent dose used by patients followed by the 60 BID dose.

Reporting group title	No drug treatment
-----------------------	-------------------

Reporting group description:

While patients remained in the Observation Period, they were not considered enrolled into the study, but as participating in an extended screening process until they were eligible for treatment.

Reporting group title	No treatment
-----------------------	--------------

Reporting group description: -

Primary: overall incidence and nature of Treatment-Emergent AEs (TEAES)

End point title	overall incidence and nature of Treatment-Emergent AEs (TEAES) ^[1]
-----------------	---

End point description:

The primary endpoint of the study was a description of the overall incidence and nature of Treatment-Emergent AEs (TEAES).

Overall, 131 patients (78.4%) of the safety population (n=167) experienced at least 1 TEAE. Of these, study drug-related TEAEs were reported in 64 patients (38.3%). 51 patients (30.5%) of the safety population experienced at least 1 treatment-emergent SAE.

End point type	Primary
----------------	---------

End point timeframe:

TEAEs occurring in the Safety Population (all patients in the TR02ext study).

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: No analysis was performed as this was a single-arm, open-label, observational study.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	167			
Units: number of events	607			

Statistical analyses

No statistical analyses for this end point

Secondary: Worst itch Numerical Rating Scale (NRS)

End point title	Worst itch Numerical Rating Scale (NRS)
-----------------	---

End point description:

Mean worst itch was decreased from baseline to the end of treatment.
No formal statistical testing has been conducted.

End point type	Secondary
----------------	-----------

End point timeframe:

All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: scales				
arithmetic mean (standard deviation)	-2.7 (± 2.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Skindex-10

End point title	Skindex-10
-----------------	------------

End point description:

Mean Skindex-10 decreased from baseline to all measured time points in the safety population. The decrease in mean Skindex-10 was most pronounced in the subgroup of patients with baseline NRS values of ≥ 7 .

No statistical analyses for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: scales				
arithmetic mean (standard deviation)	-10.56 (± 14.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Assessed Disease Severity Scale (PADS)

End point title	Patient Assessed Disease Severity Scale (PADS)
End point description:	
<p>There was a shift in PADS scores in subjects evaluated in the End of Treatment Visit in the direction of more subjects with PADS "A" scores and fewer subjects with PADS "B" and "C" scores. Of the 167 subjects in the safety population, 99 subjects completed an End of Treatment Visit. Of the 99 these subjects, 17/99 (17%) were classified by the PADS as "A"; 61/99 (62%) were classified as "B" and 21/99 (21%) were classified as "C" patients at TR02ext baseline. At the End of Treatment Visit, the distribution of the PADS scores among those 99 subjects were: 44/99 (44%) PADS "A"; 46/99 (46%) PADS "B" and 9/99 (9%) PADS "C".</p> <p>99 (8%) subjects shifted from PADS "A" to PADS "B" or from PADS "A" or PADS "B" to PADS "C".</p> <p>No statistical analyses for this end point.</p>	
End point type	Secondary
End point timeframe:	
All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.	

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: percentages	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Itch MOS Sleep Scale

End point title	Itch MOS Sleep Scale
End point description:	
<p>Mean Itch MOS decreased from baseline to the end of treatment.</p> <p>No statistical analyses for this end point.</p>	
End point type	Secondary
End point timeframe:	
All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.	

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: scales				
arithmetic mean (standard deviation)	-8.75 (± 16.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and Depression Scale (HADS) - depression

End point title	Hospital Anxiety and Depression Scale (HADS) - depression
-----------------	---

End point description:

Mean HADS Depression Subscale and Mean HADS Anxiety Subscale had decreased between the baseline and End of Treatment visits in the safety population. The decrease in mean HADS Depression and HADS Anxiety subscales were most pronounced in the subgroup of patients with baseline NRS values of ≥ 7 . No statistical analyses for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: scales				
arithmetic mean (standard deviation)	-1.15 (\pm 3.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue medications

End point title	Use of rescue medications
-----------------	---------------------------

End point description:

Less than 1/3 of the safety population recorded the use of protocol specified rescue medication during the study.

No statistical analyses for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	167			
Units: days				
arithmetic mean (standard deviation)	14 (\pm 39.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and Depression Scale (HADS) - anxiety

End point title	Hospital Anxiety and Depression Scale (HADS) - anxiety
-----------------	--

End point description:

Mean HADS Depression Subscale and Mean HADS Anxiety Subscale had decreased between the baseline and End of Treatment visits in the safety population

No statistical analyses for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

All patients with a baseline and at least one post-baseline value for an efficacy assessment were included in the summary of the change from baseline for that efficacy endpoint.

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: scales				
arithmetic mean (standard deviation)	-1.16 (\pm 3.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events were continuously evaluated throughout the study.

Adverse event reporting additional description:

Overall, 133 patients (79.6%) of the safety population (n=167) experienced at least 1 TEAE. Of these, study drug-related TEAEs were reported in 64 patients (38.3%). 54 patients (32.3%) of the safety population experienced at least 1 treatment-emergent SAE. The majority of TEAEs were grade 1 (41.6%) or grade 2 (42.5%) in intensity.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety Population
-----------------------	-------------------

Reporting group description:

The nalbuphine dose was titrated based on NRS scores between Treatment Visits 1 and 3, after which time the dose achieved (30 mg QD – 120 mg BID) as of the end of Treatment Week 3 was maintained up to an additional 21 weeks.

At the end of the titration period at week 3 of the Treatment Period the distribution of dosing was 14 subjects (8.4%) at 30 mg BID, 35 subjects (21%) at 60 mg BID, 30 subjects (18%) at 90 mg BID and 70 subjects (41.9%) at 120 mg BID. 8 subjects (4.8%) were missing data. Analyzing the distribution of study drug use over the course of the study shows that 120 mg BID was the most frequent dose used by patients followed by the 60 BID dose.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious Adverse Events were not reported out in a separate and distinct data listing for this trial.

The number of subject experiencing non-serious adverse events is 79 based on the following:

Safety population = 167

Subjects experiencing no TEAE = 34

Subjects with TEAE = 133

Subjects with serious TEAE = 54.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 167 (32.34%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant hypertension			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	4 / 167 (2.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		

Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 167 (2.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Acute pulmonary oedema			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Anticoagulation drug level below therapeutic			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous graft site haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dialysis related complication			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular graft complication			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Speech disorder			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haematoma			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arteriovenous graft site infection			
subjects affected / exposed	4 / 167 (2.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neck abscess			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			

subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis bacterial				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometritis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 167 (0.60%)		
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	0 / 167 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2014	Clinical research Protocol TR02ext v2.0 was produced for the following purposes: <ul style="list-style-type: none">• Update the Phase of the study from Phase 2 to a Phase 2/3.• Correction made to sample Numerical Rating Scale included in Appendix 4.• Correction to the EudraCT number on the cover page• To incorporate clarifications, administrative changes and correction of typographical errors throughout the protocol.
19 March 2015	Clinical research Protocol TR02ext v3.0 was produced for the following purposes: <ul style="list-style-type: none">• To add Failure-to-Improve criteria• To add a Data Safety Monitoring Board (DSMB)• To add central cardiac core laboratory read of study ECGs• To provide clarity in the transition of patients from the observation period to the treatment period• To include gender related PK and AE information from previous studies• To include summary language from the Investigator Brochure (IB) related to most frequently reported adverse events from previous studies• To provide clarity on the titration schedule and dose adjustment processes• To provide clarity on the start of AE data capture• To incorporate EU directives• To incorporate clarifications, administrative changes and correction of typographical errors throughout the protocol.
14 May 2015	Clinical research Protocol TR02ext v4.0 was produced for the following purposes: <ul style="list-style-type: none">• 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