Clinical trial results:
A RANDOMIZED PROSPECTIVE CLINICAL TRIAL TO ASSESS THE ROLE OF PROCALCITONIN-GUIDED ANTIMICROBIAL THERAPY TO REDUCE LONG-TERM INFECTIONS SEQUELAE

Summary

EudraCT number	2017-002011-33
Trial protocol	GR
Global end of trial date	20 July 2019

Results information

Result version number	v1 (current)
This version publication date	31 December 2022
First version publication date	31 December 2022

Trial information

Trial identification

Sponsor protocol code	PROGRESS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03333304
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Institute for the Study of Sepsis
Sponsor organisation address	Michalakopoulou 88 str., Athens, Greece, 11528
Public contact	President of the Board, Hellenic Institute for the Study of Sepsis, 0030 2107480662, info@sepsis.gr
Scientific contact	President of the Board, Hellenic Institute for the Study of Sepsis, 0030 2107480662, info@sepsis.gr

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	20 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to demonstrate if using one PCT-guided rule of stop of antimicrobials, the incidence of infections by C.difficile and by MDR bacteria during the next six months may be significantly decreased.

Protection of trial subjects:

Adverse events and serious adverse events were followed-up for 180 days after enrollment, which was the follow-up period for subjects in the trial. The incidence of adverse events was lower in the PCT-guided treatment group, especially diarrhea and acute kidney injury. The incidence of serious adverse events did not differ between the two groups and none was associated with the clinical trial intervention.

Background therapy:

Patients randomized in the standard-of-care treatment group receive antimicrobials according to standard practice of the attending physicians and PCT is not measured. Antimicrobials are stopped according to the local standard practice.

Evidence for comparator:

Patients randomized in the PCT-guided treatment group receive antimicrobials according to standard practice of the attending physicians and PCT is measured on day 1 (day of start of antimicrobials) and then daily starting from day 5 (96 hours from the start of antimicrobials). Antimicrobials are discontinued when PCT value is less than 80% of the initial value or it remains below 0.5 ng/ml.

Actual start date of recruitment	25 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 256
Worldwide total number of subjects	256
EEA total number of subjects	256

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)	26
From 65 to 84 years	133
85 years and over	97

Subject disposition

Recruitment

Recruitment details:

From November 2017 to January 2019, 266 patients were enrolled and randomized. Ten patients withdrew consent before the fifth day and the right to have their data processed, so the intention-to-treat population consisted of 256 patients. No one was lost during the follow-up

Pre-assignment

Screening details:

Inclusion criteria
All enrolled patients met all following inclusion criteria:
• Male or female
• In case of women, unwillingness to remain pregnant during the study period.
• Age more than or equal to 18 years
• SOFA score more than or equal to 2 points

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PCT-guidance

Arm description:

PCT group: these patients receive antimicrobials according to standard practice of the attending physicians and PCT is measured on day 1 (day of start of antimicrobials) and then daily starting from day 5 (96 hours from the start of antimicrobials). Antimicrobials are discontinued when PCT value is less than 80% of the initial value or it remains below 0.5 ng/ml.

Arm type	Experimental
Investigational medicinal product name	no IMP
Investigational medicinal product code	no IMP
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Unknown use

Dosage and administration details:

not applicable

Arm title	Standard of care

Arm description:

Standard of care: these patients receive antimicrobials according to standard practice of the attending physicians but PCT is not measured and antimicrobials are stopped according to the local standard practice.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	PCT-guidance	Standard of care
Started	125	131
Completed	125	131

Baseline characteristics

Reporting groups	
Reporting group title	PCT-guidance
Reporting group description:	
PCT group: these patients receive antimicrobials according to standard practice of the attending physicians and PCT is measured on day 1 (day of start of antimicrobials) and then daily starting from day 5 (96 hours from the start of antimicrobials). Antimicrobials are discontinued when PCT value is less than 80% of the initial value or it remains below 0.5 ng/ml.	
Reporting group title	Standard of care
Reporting group description:	
Standard of care: these patients receive antimicrobials according to standard practice of the attending physicians but PCT is not measured and antimicrobials are stopped according to the local standard practice.	

Reporting group values	PCT-guidance	Standard of care	Total
Number of subjects	125	131	256
Age categorical Units: Subjects			
Adults (18-64 years)	11	15	26
From 65-84 years	69	64	133
85 years and over	45	52	97
Age continuous			
Mean age (SD) was 78.0 (13.1) in SOC group and 79.6 (9.8) in PCT group (for the 256 patients included in ITT analysis)			
Units: years			
arithmetic mean	79.6	78	
standard deviation	± 9.8	± 13	-
Gender categorical Units: Subjects			
Female	73	69	142
Male	52	62	114

End points

End points reporting groups

Reporting group title	PCT-guidance
Reporting group description:	
PCT group: these patients receive antimicrobials according to standard practice of the attending physicians and PCT is measured on day 1 (day of start of antimicrobials) and then daily starting from day 5 (96 hours from the start of antimicrobials). Antimicrobials are discontinued when PCT value is less than 80% of the initial value or it remains below 0.5 ng/ml.	
Reporting group title	Standard of care
Reporting group description:	
Standard of care: these patients receive antimicrobials according to standard practice of the attending physicians but PCT is not measured and antimicrobials are stopped according to the local standard practice.	

Primary: Infection-associated adverse events rate for patients treated by the PCT-guided stopping rule compared to patients treated by standard of care

End point title	Infection-associated adverse events rate for patients treated by the PCT-guided stopping rule compared to patients treated by standard of care
End point description:	
The rate of infection-associated adverse events until day 180 is the primary outcome. This is an endpoint composed by any of the following: new case of Clostridioides difficile infection; new case of infection by multidrug-resistant organisms (MDRO); and death associated with either MDRO or Clostridioides difficile baseline infection	
End point type	Primary
End point timeframe:	
180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: events	9	20		

Statistical analyses

Statistical analysis title	primary endpoint analysis
Comparison groups	Standard of care v PCT-guidance
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.98

Secondary: 28-day mortality	
End point title	28-day mortality
End point description: all-cause mortality	
End point type	Secondary
End point timeframe: 28 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: deaths	19	37		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.89

Secondary: 180 day mortality	
End point title	180 day mortality
End point description: all cause mortality	

End point type	Secondary
End point timeframe: 180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: deaths	38	50		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.19

Secondary: Rate of new infections by multidrug-resistant organisms (MDRO)

End point title	Rate of new infections by multidrug-resistant organisms (MDRO)
End point description: New infections by multidrug-resistant organisms	
End point type	Secondary
End point timeframe: 180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: patients	5	8		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.01

Secondary: Rate of new infection by Clostridioides difficile (CDI)

End point title	Rate of new infection by Clostridioides difficile (CDI)
End point description:	
End point type	Secondary
End point timeframe:	
180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: patients	6	12		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.38

Secondary: Length of antimicrobial therapy

End point title	Length of antimicrobial therapy

End point description:

End point type	Secondary

End point timeframe:

180 days

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: days	5	10		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Gut colonization rate by multidrug-resistant organisms (MDRO)

End point title	Gut colonization rate by multidrug-resistant organisms (MDRO)

End point description:

End point type	Secondary
End point timeframe: 180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: patients	15	13		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.7

Secondary: Gut colonization rate by Clostridioides difficile

End point title	Gut colonization rate by Clostridioides difficile
End point description:	

End point type	Secondary
End point timeframe: 180 days	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: patients	14	13		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	PCT-guidance v Standard of care
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.54

Secondary: Cost of hospitalization	
End point title	Cost of hospitalization
End point description:	
End point type	Secondary
End point timeframe:	
Length of hospitalization	

End point values	PCT-guidance	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: euros	957	1183		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	Standard of care v PCT-guidance

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

180 days

Adverse event reporting additional description:

Adverse events (AEs) and Serious Adverse Events (SAEs) will be collected from baseline until the last patient's evaluation. while patients were hospitalized, these events were collected from medical records. WHa discharged, by phone calls to patients.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5

Reporting groups

Reporting group title	PCT group
Reporting group description: -	
Reporting group title	SOC group

Reporting group description: -

Serious adverse events	PCT group	SOC group	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 125 (54.40%)	71 / 131 (54.20%)	
number of deaths (all causes)	38	50	
number of deaths resulting from adverse events	38	50	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebral metastases			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hematoma			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Cholecystectomy			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Fever			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Orchiepididymitis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration penumonia			
subjects affected / exposed	1 / 125 (0.80%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Low respiratory tract infection			
subjects affected / exposed	4 / 125 (3.20%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonectomy			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 125 (0.80%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac decompensation			
subjects affected / exposed	1 / 125 (0.80%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transient ischaemic attack			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 125 (0.80%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spasms			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Clostridium difficile infection			

subjects affected / exposed	2 / 125 (1.60%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheter infection			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leishmaniasis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapse infection			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella gastroenteritis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	36 / 125 (28.80%)	48 / 131 (36.64%)	
occurrences causally related to treatment / all	0 / 36	0 / 48	
deaths causally related to treatment / all	0 / 31	0 / 43	
Urinary tract infection			
subjects affected / exposed	6 / 125 (4.80%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			

subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	PCT group	SOC group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 125 (51.20%)	83 / 131 (63.36%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	2 / 125 (1.60%)	0 / 131 (0.00%)	
occurrences (all)	2	0	
Thrombophlebitis			
subjects affected / exposed	3 / 125 (2.40%)	2 / 131 (1.53%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Hypersalivation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy			
subjects affected / exposed	5 / 125 (4.00%)	1 / 131 (0.76%)	
occurrences (all)	5	1	
Autoimmune disease			
subjects affected / exposed	1 / 125 (0.80%)	1 / 131 (0.76%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			

Pleural effusion			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Rhinorrhagia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Singultus			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 125 (1.60%)	1 / 131 (0.76%)	
occurrences (all)	2	1	
Investigations			
Troponin increased			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 125 (0.80%)	2 / 131 (1.53%)	
occurrences (all)	1	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 125 (0.80%)	1 / 131 (0.76%)	
occurrences (all)	1	1	
NSTEMI	Additional description: Non-ST-Elevation Myocardial Infarction		
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral edema			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Spasticity			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 125 (0.80%)	8 / 131 (6.11%)	
occurrences (all)	1	8	
Bleeding			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Pancytopenia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	1 / 125 (0.80%)	3 / 131 (2.29%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	15 / 125 (12.00%)	16 / 131 (12.21%)	
occurrences (all)	15	16	
Gastrointestinal hemorrhage	Additional description: gastrointestinal bleeding		
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 125 (0.00%)	2 / 131 (1.53%)	
occurrences (all)	0	2	
Diarrhea			
subjects affected / exposed	24 / 125 (19.20%)	48 / 131 (36.64%)	
occurrences (all)	24	48	
Hepatobiliary disorders			
Elevated aminotransferases			
subjects affected / exposed	2 / 125 (1.60%)	4 / 131 (3.05%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			

Decubitus			
subjects affected / exposed	1 / 125 (0.80%)	2 / 131 (1.53%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Microhematuria			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	9 / 125 (7.20%)	23 / 131 (17.56%)	
occurrences (all)	9	23	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Arthritis			
subjects affected / exposed	2 / 125 (1.60%)	0 / 131 (0.00%)	
occurrences (all)	2	0	
Myositis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 131 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	4 / 125 (3.20%)	3 / 131 (2.29%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Hypoalbuminemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 131 (0.76%)	
occurrences (all)	0	1	
Electrolyte disorder			

subjects affected / exposed occurrences (all)	16 / 125 (12.80%) 16	31 / 131 (23.66%) 31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2018	add of a new site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32757963