Clinical trial results:
A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)

Summary

EudraCT number	2014-004942-91
Trial protocol	GB AT HU DE BE IT ES CZ
Global end of trial date	19 April 2017

Results information

Result version number	v1 (current)
This version publication date	19 April 2018
First version publication date	19 April 2018

Trial information

Trial identification

Sponsor protocol code	1423M0634

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Shionogi Ltd.
Sponsor organisation address	33 Kingsway, London, United Kingdom, WC2B 6UF
Public contact	Regulatory Affairs., Shionogi Ltd., +44 20 3053 4200, 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	19 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2017
Global end of trial reached?	Yes
Global end of trial date	19 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in patients with CLD who are undergoing elective invasive procedures

Protection of trial subjects:

The study was conducted in accordance with all appropriate regulatory requirements and under the IEC-approved protocol, as well as in accordance with current International Council for Harmonisation (ICH), Good Clinical Practice (GCP), all appropriate subject privacy requirements, and the ethical principles outlined in the Declaration of Helsinki (1996).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2015
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: 15
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Israel: 27
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Thailand: 6

Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	215
EEA total number of subjects	94

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)	172
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A multi-center study conducted at 138 sites in 22 countries. A total of 215 Subjects were enrolled into the study. Number of Subjects Planned: 200 (100 per treatment group)
Number of subjects Randomized: 215 (lusutrombopag, 108; placebo, 107).

Pre-assignment

Screening details:

A screening period (up to 28 days prior to randomization).
322 subjects were screened and 215 randomised.
During the screening visit, informed consent was obtained prior to any study-related procedures.

Pre-assignment period milestones

Number of subjects started	322[1]
Number of subjects completed	215

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Other: 107

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The world-wide number reported is equal to the number of randomised patients and not to the pre-assignment number.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment period with lusutrombopag

Arm description:

A treatment period of 7 days (Days 1 to 7 during which study drug was to be administered for 4 to 7 days). Once-daily treatment with lusutrombopag 3 mg or placebo was to commence on Day 1 and continue for up to 7 days. Administration of the study drug on Day 2 was to be performed ≥ 12 hours after administration on Day 1. Platelet count was to be determined on Days 5, 6, and 7 prior to the administration of study drug.

Arm type	Experimental
Investigational medicinal product name	Lusutrombopag
Investigational medicinal product code	S-888711
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 mg lusutrombopag or placebo once daily.

Arm title	Treatment with Placebo

Arm description:

A treatment period of 7 days (Days 1 to 7 during which study drug was to be administered for 4 to 7 days). Once-daily treatment with lusutrombopag 3 mg or placebo was to commence on Day 1 and continue for up to 7 days. Administration of the study drug on Day 2 was to be performed ≥ 12 hours after administration on Day 1. Platelet count was to be determined on Days 5, 6, and 7 prior to the

administration of study drug.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 mg lusutrombopag or placebo once daily.

Number of subjects in period 1	Treatment period with lusutrombopag	Treatment with Placebo
Started	108	107
Completed	98	102
Not completed	10	5
Adverse event, serious fatal	3	-
Consent withdrawn by subject	4	3
Adverse event, non-fatal	-	1
Other	2	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period
Reporting group description:	
Overall, 200 subjects (93.0%) completed the study, including 98 subjects (90.7%) in the lusutrombopag group and 102 subjects (95.3%) in the placebo group.	

Reporting group values	Treatment Period	Total	
Number of subjects	215	215	
Age categorical Units: Subjects			
Adults (18-64 years)	172	172	
From 65-84 years	43	43	
Age continuous Units: years			
arithmetic mean	55.7		
full range (min-max)	19 to 83	-	
Gender categorical Units: Subjects			
Female	81	81	
Male	134	134	

End points

End points reporting groups

Reporting group title	Treatment period with lusutrombopag
Reporting group description:	
A treatment period of 7 days (Days 1 to 7 during which study drug was to be administered for 4 to 7 days). Once-daily treatment with lusutrombopag 3 mg or placebo was to commence on Day 1 and continue for up to 7 days. Administration of the study drug on Day 2 was to be performed ≥ 12 hours after administration on Day 1. Platelet count was to be determined on Days 5, 6, and 7 prior to the administration of study drug.	
Reporting group title	Treatment with Placebo
Reporting group description:	
A treatment period of 7 days (Days 1 to 7 during which study drug was to be administered for 4 to 7 days). Once-daily treatment with lusutrombopag 3 mg or placebo was to commence on Day 1 and continue for up to 7 days. Administration of the study drug on Day 2 was to be performed ≥ 12 hours after administration on Day 1. Platelet count was to be determined on Days 5, 6, and 7 prior to the administration of study drug.	

Primary: Proportion of subjects who required no platelet transfusion

End point title	Proportion of subjects who required no platelet transfusion
End point description:	
Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure.	
End point type	Primary
End point timeframe:	
From randomization through 7 days after the primary invasive procedure.	

End point values	Treatment period with lusutrombopag	Treatment with Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	107		
Units: Number of subjects	70	31		

Statistical analyses

Statistical analysis title	Intention to Treat (ITT)
Comparison groups	Treatment period with lusutrombopag v Treatment with Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs (both serious and non-serious) were to be collected throughout the study from the time of informed consent until the patient's final follow-up visit or 28 days after the last dose of study medication, whichever was later.

Adverse event reporting additional description:

Adverse events were classified by system organ class (SOC) and preferred term using the MeDRA. Of the AEs reported, TEAEs (defined as those reported after administration of the first dose of study drug) were used for the analysis of safety. AEs could be spontaneously reported by the subject or elicited from non-leading questions.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	S-888711 3 mg

Reporting group description:

A total of 109 TEAEs were reported in 51 of 107 subjects (47.7%) in Lusutrombopag groups. Headache was the only TEAE that occurred at an incidence of 5% or more in the lusutrombopag group.

Reporting group title	Placebo

Reporting group description:

134 TEAEs were reported in 52 of 107 subjects (48.6%) in the placebo group. No safety concerns for lusutrombopag 3 mg compared with placebo were raised.

Serious adverse events	S-888711 3 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 107 (6.54%)	7 / 107 (6.54%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vessel perforation			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (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			
Multi-organ failure			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid retention			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	S-888711 3 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 107 (43.93%)	51 / 107 (47.66%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Focal nodular hyperplasia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Hepatic neoplasm			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Colon adenoma			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	2	1	
Hot flush			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	
Cryoglobulinaemia			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Hypertensive crisis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Varicose vein			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 107 (2.80%)	7 / 107 (6.54%)	
occurrences (all)	3	7	
Oedema peripheral			
subjects affected / exposed	3 / 107 (2.80%)	4 / 107 (3.74%)	
occurrences (all)	3	5	
Pyrexia			
subjects affected / exposed	3 / 107 (2.80%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Asthenia			
subjects affected / exposed	2 / 107 (1.87%)	2 / 107 (1.87%)	
occurrences (all)	2	2	
Chest pain			
subjects affected / exposed	2 / 107 (1.87%)	1 / 107 (0.93%)	
occurrences (all)	2	1	
Chest discomfort			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Metaplasia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences (all)	0	2	
General physical health deterioration			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences (all)	0	2	
Hyperthermia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Thirst			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Cough			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Laryngeal discomfort			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	
Agitation			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Tension			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Portal vein flow decreased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	3 / 107 (2.80%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Procedural complication			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Postoperative fever			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Traumatic haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Eyelid injury			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 107 (5.61%)	2 / 107 (1.87%)	
occurrences (all)	7	2	
Hepatic encephalopathy			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences (all)	1	2	
Encephalopathy			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	
occurrences (all)	2	0	
Myelopathy			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Neurological decompensation			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	
Splenomegaly			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Spleen congestion			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Eyelid haematoma			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 107 (1.87%)	4 / 107 (3.74%)	
occurrences (all)	2	4	
Upper Abdominal pain			
subjects affected / exposed	2 / 107 (1.87%)	3 / 107 (2.80%)	
occurrences (all)	2	4	
Ascites			
subjects affected / exposed	2 / 107 (1.87%)	3 / 107 (2.80%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	3 / 107 (2.80%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Duodenal ulcer			
subjects affected / exposed	2 / 107 (1.87%)	2 / 107 (1.87%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	2 / 107 (1.87%)	1 / 107 (0.93%)	
occurrences (all)	2	1	
Abdominal pain lower			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	

Hiatus hernia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Anorectal varices			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Peptic ulcer			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	5 / 107 (4.67%)	5 / 107 (4.67%)	
occurrences (all)	6	5	
Hepatobiliary disorders			
Portal vein thrombosis			

subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences (all)	0	2	
Acute hepatic failure			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Portal hypertension			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Cholecystitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Cholestasis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Retrograde portal vein flow			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences (all)	1	2	
Ecchymosis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	

Hand dermatitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 107 (1.87%)	1 / 107 (0.93%)	
occurrences (all)	2	1	
Arthralgia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Myofascial pain syndrome			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 107 (2.80%)	0 / 107 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences (all)	1	1	

Clostridium difficile colitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Urethritis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Anal abscess			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Helicobacter infection			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Non reported.

Notes: