



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 |
| Scientific contact | Dr Nico Merante, Vice President, Clinical Development - Europe, Shionogi Ltd., +44 020 3053 4200, shionogiclintrials-admin@shionogi.co.jp |

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 \geq 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 \geq 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 full range (min-max) | 55.7 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 MedDRA. 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 occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Pharyngeal haemorrhage subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Laryngeal discomfort subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 1 / 107 (0.93%) 1 | |
| Agitation subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Tension subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Investigations | | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 2 / 107 (1.87%) 2 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 1 / 107 (0.93%) 1 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 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 occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Fall subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Postoperative fever subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Traumatic haemorrhage subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Eyelid injury subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 7 | 2 / 107 (1.87%) 2 | |
| Hepatic encephalopathy subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 2 / 107 (1.87%) 2 | |
| Encephalopathy subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Somnolence subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 0 / 107 (0.00%) 0 | |
| Myelopathy | | | |

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

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Eyelid haematoma subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 4 / 107 (3.74%) 4 | |
| Upper Abdominal pain subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 3 / 107 (2.80%) 4 | |
| Ascites subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 3 / 107 (2.80%) 3 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 3 | 2 / 107 (1.87%) 2 | |
| Duodenal ulcer subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 2 / 107 (1.87%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 2 / 107 (1.87%) 2 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 1 / 107 (0.93%) 1 | |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 1 / 107 (0.93%) 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 occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 0 / 107 (0.00%) 0 | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 2 / 107 (1.87%) 2 | 1 / 107 (0.93%) 1 | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Groin pain subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Myofascial pain syndrome subjects affected / exposed occurrences (all) | 0 / 107 (0.00%) 0 | 1 / 107 (0.93%) 1 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 107 (2.80%) 3 | 0 / 107 (0.00%) 0 | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 107 (0.93%) 1 | 1 / 107 (0.93%) 1 | |

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

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| Non reported. |
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Notes: