



Clinical trial results:

An open-label, multi-national, multi-center, single-arm, uncontrolled, longterm extension study of orally administered riociguat in patients with symptomatic pulmonary arterial hypertension (PAH) who received riociguat in a Bayer clinical trial

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-000501-36 |
| Trial protocol | FR IT |
| Global end of trial date | 15 September 2025 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 27 February 2026 |
| First version publication date | 27 February 2026 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY63-2521/18694 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02759419 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 October 2025 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2025 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 September 2025 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To provide riociguat therapy to eligible patients with PAH originating from the Bayer-sponsored trials 12935 PATENT-2 or 16719 RESPITE who are currently or recently treated in these trials until lack of patient benefit as assessed by investigator, or commercial availability and reimbursement.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 16 June 2016 |
| 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 | France: 7 |
| Country: Number of subjects enrolled | Korea, Republic of: 11 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 7 |

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) | 15 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study centers in 2 countries (5 in France and 4 in South Korea) between 16 June 2016 (first participant first visit) consent) and 15 September 2025 (last participant last visit).

Pre-assignment

Screening details:

A total of 18 participants were enrolled and no participant failed screening.

All 18 participants received study intervention. 12 Participants did not complete the treatment phase.

Period 1

| | |
|------------------------------|--------------------------|
| Period 1 title | overall (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|-------------------------|
| Arm title | Riociguat (BAY 63-2521) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Riociguat (BAY 63-2521) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

0.5 to 2.5 mg in 0.5 mg increments (according to individually adapted optimal dose) administered three times daily

| Number of subjects in period 1 | Riociguat (BAY 63-2521) |
|--------------------------------|-------------------------|
| Started | 18 |
| Completed | 6 |
| Not completed | 12 |
| Consent withdrawn by subject | 1 |
| Physician decision | 5 |
| Adverse event, non-fatal | 1 |
| Death | 4 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Riociguat (BAY 63-2521) |
|-----------------------|-------------------------|

Reporting group description: -

| Reporting group values | Riociguat (BAY 63-2521) | Total | |
|---|-------------------------|-------|--|
| Number of subjects | 18 | 18 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 15 | 15 | |
| From 65-84 years | 3 | 3 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 12 | |
| Male | 6 | 6 | |

End points

End points reporting groups

| | |
|--------------------------------|-------------------------|
| Reporting group title | Riociguat (BAY 63-2521) |
| Reporting group description: - | |

Primary: Number of Participants with treatment emergent adverse events (TEAE)s

| | |
|-----------------|--|
| End point title | Number of Participants with treatment emergent adverse events (TEAE)s ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

From first intake of study medication until end of study.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.

| End point values | Riociguat (BAY 63-2521) | | | |
|---|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: Participants | | | | |
| any TEAE | 18 | | | |
| mild TEAE | 3 | | | |
| moderate TEAE | 6 | | | |
| severe TEAE | 9 | | | |
| any treatment-related TEAE | 5 | | | |
| mild treatment-related TEAE | 2 | | | |
| moderate treatment-related TEAE | 2 | | | |
| severe treatment-related TEAE | 1 | | | |
| any TEAE leading to discontinuation of intervention | 5 | | | |
| any TEAE leading to modification of intervention | 0 | | | |
| any TEAE of special interest | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected after signing the informed consent until 30 days after end of study treatment over a period of approximately five years.

Adverse event reporting additional description:

12 participants (66.7%) reported at least 1 treatment-emergent SAE (cross ref to table) including 4 deaths. None of the treatment emergent SAE/death was assessed as treatment-related.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 28.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Full Analysis Set |
|-----------------------|-------------------|

Reporting group description:

All 18 participants, who have been included in the study and have received at least one dose of the study treatment.

| Serious adverse events | Full Analysis Set | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 18 (66.67%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | 4 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm recurrence | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|--|-----------------|--|--|
| Peritoneal catheter insertion | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Salpingo-oophorectomy bilateral | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoperitoneum | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|--|--|
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Full Analysis Set | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 18 (100.00%) | | |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Liver transplant | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Administration site pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 4 | | |
| Chest pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Oedema | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Pelvic cyst | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | | |
| occurrences (all) | 5 | | |
| Epistaxis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 4 | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Orthopnoea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Snoring | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| N-terminal prohormone brain natriuretic peptide increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 | | |
| Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) Atrial fibrillation subjects affected / exposed occurrences (all) Right ventricular failure subjects affected / exposed occurrences (all) Ventricular tachycardia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2 2 / 18 (11.11%) 3 1 / 18 (5.56%) 1 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Essential tremor subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all) Syncope | 3 / 18 (16.67%) 6 1 / 18 (5.56%) 1 6 / 18 (33.33%) 7 1 / 18 (5.56%) 1 | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 3 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Glaucoma | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Macular degeneration | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Conjunctival oedema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain upper | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Ascites | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 18 (38.89%) | | |
| occurrences (all) | 11 | | |
| Functional gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Melaena | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Oesophagitis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Tooth disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 3 | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Congestive hepatopathy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Cold sweat | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Skin reaction | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------------|--|--|
| Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Back pain subjects affected / exposed occurrences (all) | 3 / 18 (16.67%) 3 | | |
| Coccydynia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 18 (16.67%) 3 | | |
| Pain in jaw subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Torticollis subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Infections and infestations | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| COVID-19 | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | | |
| occurrences (all) | 4 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 4 | | |

| | | | |
|---|----------------------|--|--|
| Septic shock subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 3 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Folate deficiency subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Gout subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Iron deficiency subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 17 August 2016 | inclusion of a new exclusion criterion |
| 10 March 2017 | Opening of the study for patients from study 18588 (REPLACE) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported