



Clinical trial results:

An Extended Access Program to Assess Long-Term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-004365-16 |
| Trial protocol | ES BE CZ GB DE |
| Global end of trial date | 30 September 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 17 October 2021 |
| First version publication date | 17 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 402-C-1602 |
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Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03068130 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Reata Pharmaceuticals |
| Sponsor organisation address | 5320 Legacy Drive, Plano, United States, 75024 |
| Public contact | Clinical Study Manager, Reata Pharmaceuticals, Inc., 972 8652219, 408C1602DNK@reatapharma.com |
| Scientific contact | Clinical Study Manager, Reata Pharmaceuticals, Inc., 972 8652219, 408C1602DNK@reatapharma.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 | 03 August 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 September 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This extended access (open label) study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl. Qualified patients will receive 10 mg of bardoxolone methyl once daily until the drug is available through commercial channels or until patient withdrawal, whichever is sooner. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Protection of trial subjects:

The study sites will be monitored remotely by the CRO periodically during the study to ensure that all aspects of the protocol will be followed and will include an electronic data collection which has a set of automatic data checks with data queries for programmed data collection. There will be monitoring of study site by telephone to ensure that the drug supplies have been provided and protocol instructions are well understood and applied. The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Council for Harmonisation (ICH) guideline E6(R1): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 18 April 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Argentina: 23 |
| Country: Number of subjects enrolled | Australia: 13 |
| Country: Number of subjects enrolled | Brazil: 4 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Japan: 12 |
| Country: Number of subjects enrolled | Mexico: 11 |
| Country: Number of subjects enrolled | Philippines: 5 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 161 |
| Worldwide total number of subjects | 261 |
| EEA total number of subjects | 20 |

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) | 171 |
| From 65 to 84 years | 90 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Treatment-compliant patients who are participating in qualifying ongoing studies and have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl.

Pre-assignment

Screening details:

This is an extended access (Open label) study assessing the long-term safety and tolerability of bardoxolone methyl in patients with PH who previously participated in qualifying clinical studies 402-C-1504 and 402-C-1302 (also referred to as previous qualifying studies of Study 1602) with bardoxolone methyl. All patients received bardoxolone methyl

Period 1

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

Arms

| | |
|-----------|--|
| Arm title | Experimental: Bardoxolone Methyl 10 mg |
|-----------|--|

Arm description:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bardoxolone methyl capsules 10mg |
| Investigational medicinal product code | RTA 402 |
| Other name | BARDOXOLONE METHYL, CDDO-Me, CDDO-Methyl Ester, NSC 713200, Chemical Name: Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

| Number of subjects in period 1 | Experimental: Bardoxolone Methyl 10 mg |
|--|--|
| Started | 261 |
| Completed | 0 |
| Not completed | 261 |
| Adverse event, serious fatal | 14 |
| Administrative Reasons | 3 |
| Consent withdrawn by subject | 26 |
| Adverse event, non-fatal | 19 |
| Protocol Specified Withdrawal Criterion | 1 |
| Study Terminated by Sponsor | 194 |

| | |
|-------------------|---|
| Lost to follow-up | 4 |
|-------------------|---|

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 261 | 261 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Experimental: Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically. | | | |
| Units: years | | | |
| arithmetic mean | 56.7 | | |
| standard deviation | ± 12.79 | - | |
| Gender categorical | | | |
| Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically. | | | |
| Units: Subjects | | | |
| Female | 221 | 221 | |
| Male | 40 | 40 | |
| Ethnic Group | | | |
| Experimental: Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 22 | 22 | |
| Native Hawaiian or Pacific Islander | 0 | 0 | |
| Black or African American | 30 | 30 | |
| More than one race | 204 | 204 | |
| Unknown or Not Reported | 5 | 5 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Experimental: Bardoxolone Methyl 10 mg |
| Reporting group description: Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically. | |

Primary: Long term safety as measured by incidence and severity of adverse events during the duration of the study

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|-----------------|--|
| End point title | Long term safety as measured by incidence and severity of adverse events during the duration of the study ^[1] |
|-----------------|--|

End point description:

Severity was defined using the following definitions: Mild: Symptoms causing no or minimal interference with usual social and functional activities; Moderate: Symptoms causing greater than minimal interference with usual social and functional activities; Severe: Symptoms causing inability to perform usual social and functional activities.

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

End point timeframe:

From time of first dose until the final visit, up to 172 weeks

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: This extended access (open label) study assessed the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl. The Primary endpoint was long term safety as measured by incidence and severity of adverse events during the duration of the study. As such, no additional statistical analysis was performed.

| End point values | Experimental: Bardoxolone Methyl 10 mg | | | |
|---|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 261 | | | |
| Units: Count of Participants | | | | |
| number (not applicable) | | | | |
| Number of subjects with at least one AE | 232 | | | |
| Number of subjects with a related AE | 89 | | | |
| Number of subjects with a serious AE | 106 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time from the date of a participant's first dose to his or her last participation or event date, a maximum of 172 weeks

Adverse event reporting additional description:

All AEs/SAEs from the time of admin of the first dose until final visit were to be reported. AEs/SAEs occurring within 30 days after last dose were considered treatment emergent. For SAEs, the PI was to follow the patient until the SAE subsided or until the condition became chronic in nature, stabilized (persistent impairment) or the patient died.

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| Assessment type | Systematic |
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Dictionary used

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

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|--------------------|------|
| Dictionary version | 19.0 |
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Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Experimental: Bardoxolone Methyl 10 mg |
|-----------------------|--|

Reporting group description:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

| Serious adverse events | Experimental: Bardoxolone Methyl 10 mg | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 106 / 261 (40.61%) | | |
| number of deaths (all causes) | 17 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Salivary gland cancer | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

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|--|-----------------|--|--|
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Shock | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 4 / 261 (1.53%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Asthma | | | |

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|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea exertional | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Interstitial lung disease | | | | |
| subjects affected / exposed | 3 / 261 (1.15%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary arterial hypertension | | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | | |
| occurrences causally related to treatment / all | 2 / 16 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary hypertension | | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 5 / 261 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 261 (1.15%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Norovirus test positive | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Drug administration error | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Environmental exposure | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eschar | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laceration | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Angina unstable | | | |

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|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arteriosclerosis coronary artery | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial flutter | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 4 / 261 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Cardiac failure acute | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac failure congestive | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardio-respiratory arrest | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiogenic shock | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dilatation ventricular | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 3 / 261 (1.15%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right ventricular dysfunction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Systolic dysfunction | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebellar artery thrombosis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolic stroke | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lateral medullary syndrome | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Lumbar radiculopathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal epidural haematoma | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasculitis cerebral | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Agranulocytosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dental cyst | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Faecaloma | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 3 / 261 (1.15%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrooesophageal reflux disease | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoids thrombosed | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mallory-Weiss syndrome | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal motility disorder | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| 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 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue | | | |

| | | | | |
|---|-----------------|--|--|--|
| disorders | | | | |
| Bursitis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Costochondritis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal pain | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myalgia | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoarthritis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Scleroderma | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal deformity | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Systemic lupus erythematosus | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |

| | | | | |
|---|-----------------|--|--|--|
| Appendicitis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atypical pneumonia | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bursitis infective | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 4 / 261 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis staphylococcal | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile infection | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea infectious | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ecthyma | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemophilus infection | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious colitis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 4 / 261 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis | | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | | |
| occurrences causally related to treatment / all | 0 / 13 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia staphylococcal | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 261 (1.15%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 261 (0.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Experimental: Bardoxolone Methyl 10 mg | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 198 / 261 (75.86%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 12 / 261 (4.60%) | | |
| occurrences (all) | 12 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 261 (2.30%) | | |
| occurrences (all) | 6 | | |
| Fatigue | | | |
| subjects affected / exposed | 19 / 261 (7.28%) | | |
| occurrences (all) | 19 | | |
| Non-cardiac chest pain | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 10 / 261 (3.83%) | | |
| occurrences (all) | 10 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 261 (6.13%) | | |
| occurrences (all) | 169 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 261 (3.07%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 25 / 261 (9.58%) | | |
| occurrences (all) | 25 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 25 / 261 (9.58%) | | |
| occurrences (all) | 25 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Epistaxis | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 6 / 261 (2.30%) | | |
| occurrences (all) | 6 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 8 / 261 (3.07%) | | |
| occurrences (all) | 8 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Psychiatric disorders | | | |

| | | | |
|---|--|--|--|
| Insomnia subjects affected / exposed occurrences (all) | 8 / 261 (3.07%) 8 | | |
| Investigations Brain natriuretic peptide increased subjects affected / exposed occurrences (all) N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) | 6 / 261 (2.30%) 6 21 / 261 (8.05%) 21 16 / 261 (6.13%) 16 | | |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 6 / 261 (2.30%) 6 | | |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 12 / 261 (4.60%) 12 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) | 22 / 261 (8.43%) 22 26 / 261 (9.96%) 26 9 / 261 (3.45%) 9 | | |
| Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) | 14 / 261 (5.36%) 14 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------|--|--|
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 261 (3.83%) | | |
| occurrences (all) | 10 | | |
| Constipation | | | |
| subjects affected / exposed | 11 / 261 (4.21%) | | |
| occurrences (all) | 11 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 261 (15.71%) | | |
| occurrences (all) | 41 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |
| Nausea | | | |
| subjects affected / exposed | 31 / 261 (11.88%) | | |
| occurrences (all) | 31 | | |
| Vomiting | | | |
| subjects affected / exposed | 12 / 261 (4.60%) | | |
| occurrences (all) | 12 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |
| Back pain | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 33 / 261 (12.64%) | | |
| occurrences (all) | 33 | | |
| Musculoskeletal pain | | | |

| | | | |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Myalgia | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |
| Neck pain | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 17 / 261 (6.51%) | | |
| occurrences (all) | 17 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 21 / 261 (8.05%) | | |
| occurrences (all) | 21 | | |
| Cellulitis | | | |
| subjects affected / exposed | 8 / 261 (3.07%) | | |
| occurrences (all) | 8 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 10 / 261 (3.83%) | | |
| occurrences (all) | 10 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Influenza | | | |
| subjects affected / exposed | 14 / 261 (5.36%) | | |
| occurrences (all) | 14 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 8 / 261 (3.07%) | | |
| occurrences (all) | 8 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |

| | | | |
|------------------------------------|-------------------|--|--|
| Pneumonia | | | |
| subjects affected / exposed | 11 / 261 (4.21%) | | |
| occurrences (all) | 11 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | | |
| occurrences (all) | 9 | | |
| Sinusitis | | | |
| subjects affected / exposed | 22 / 261 (8.43%) | | |
| occurrences (all) | 22 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 51 / 261 (19.54%) | | |
| occurrences (all) | 51 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 30 / 261 (11.49%) | | |
| occurrences (all) | 30 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 15 / 261 (5.75%) | | |
| occurrences (all) | 15 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | | |
| occurrences (all) | 13 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 7 / 261 (2.68%) | | |
| occurrences (all) | 7 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 6 / 261 (2.30%) | | |
| occurrences (all) | 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--------------------------------|
| 27 October 2016 | Protocol Version 1.0 |
| 05 January 2017 | Protocol Version 2.0 |
| 05 January 2017 | Protocol Version 2.1 (Japan) |
| 01 March 2017 | Protocol Version 2.2 (Japan) |
| 09 May 2017 | Protocol Version 2.1 (UK) |
| 23 June 2017 | Protocol Version 2.2 (Germany) |
| 16 July 2018 | Protocol Version 3.0 |
| 16 July 2018 | Protocol Version 3.1 (UK) |
| 16 July 2018 | Protocol Version 3.1 (Germany) |
| 25 July 2018 | Protocol Version 3.1 (Japan) |
| 11 July 2019 | Protocol Version 3.2 (Germany) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|-------------------|---|---|
| 30 September 2020 | Due to the COVID-19 pandemic and consideration of the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases, and on recommendation from the parent study's DSMB (402-C-1504), the Sponsor decided to stop the Phase 3 Study (1504) in patients with CTD-PAH. Patients with CTD-PAH have compromised cardiopulmonary function, are often receiving immunosuppressants, and are at an inherently high risk of adverse outcomes in the event of infection. The Sponsor concluded that continued exposure of these high-risk patients to clinic or in-person visits presented an unacceptable risk. The 1504 parent study was not stopped as a result of any bardoxolone methyl-related safety concern, and the DSMB did not reported any treatment-related safety concerns. There were no deaths in the bardoxolone methyl arm of study 1504, and fewer patients reported serious adverse events (SAE) in the bardoxolone methyl arm compared to the placebo arm within the 1504 study. While no futility analyses were performed, an initial review of available efficacy data provided by the DSMB suggested that Study 1504 was unlikely to meet the primary endpoint of improvement in 6MWD compared to placebo at Week 24. Concomitant with the decision to close Study 1504, the Sponsor also closed Study this study 402-C-1602. | - |
|-------------------|---|---|

Notes:

Limitations and caveats

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

Early termination of this study due to COVID-19 Pandemic and in consideration of the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases.

Notes: