



## Clinical trial results:

### An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients With Chronic Kidney Disease

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-003253-24 |
| Trial protocol           | ES FR BE DE CZ |
| Global end of trial date | 23 August 2023 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 06 March 2024 |
| First version publication date | 06 March 2024 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 402-C-1803 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03749447 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Reata, a wholly owned subsidiary of Biogen  |
| Sponsor organisation address | 225 Binney Street, Cambridge, United States, 02142  |
| Public contact               | Study Medical Director, Reata, a wholly owned subsidiary of Biogen, clinicaltrials@biogen.com |
| Scientific contact           | Study Medical Director, Reata, a wholly owned subsidiary of Biogen, clinicaltrials@biogen.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 July 2023 |
| Is this the analysis of the primary completion data? | No           |

|                                  |                |
|----------------------------------|----------------|
| Global end of trial reached?     | Yes            |
| Global end of trial date         | 23 August 2023 |
| Was the trial ended prematurely? | Yes            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorised representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorised representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 08 March 2019 |
| 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 | United States: 215 |
| Country: Number of subjects enrolled | Australia: 10      |
| Country: Number of subjects enrolled | Japan: 29          |
| Country: Number of subjects enrolled | Spain: 6           |
| Country: Number of subjects enrolled | France: 6          |
| Country: Number of subjects enrolled | Puerto Rico: 4     |
| Worldwide total number of subjects   | 270                |
| EEA total number of subjects         | 12                 |

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) | 9   |
| Adults (18-64 years)      | 239 |
| From 65 to 84 years       | 22  |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in the United States, Australia, Japan, Spain, Puerto Rico and France from 08 March 2019 to 23 August 2023.

### Pre-assignment

Screening details:

A total of 270 eligible participants who participated in the previous qualifying studies i.e., 402-C-1603 (NCT03019185) and 402-C-1808 (NCT03918447) of bardoxolone methyl were enrolled in this study. Data was summarized as per the treatment received in the previous qualifying studies.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|                              |                                     |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes                                 |
| <b>Arm title</b>             | Prior Placebo to Bardoxolone Methyl |

Arm description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility urine albumin to creatinine ratio (UACR) >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Bardoxolone methyl |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Capsule            |
| Routes of administration               | Oral use           |

Dosage and administration details:

Administered as specified in the treatment arm.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Prior Bardoxolone Methyl to Bardoxolone Methyl |
|------------------|--|

Arm description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Bardoxolone methyl |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Capsule            |
| Routes of administration               | Oral use           |

Dosage and administration details:

Administered as specified in the treatment arm.

| Number of subjects in period 1                | Prior Placebo to<br>Bardoxolone Methyl | Prior Bardoxolone<br>Methyl to<br>Bardoxolone Methyl |
|---|--|--|
|   |  |  |
| Started                                       | 143                                    | 127  |
| Completed                                     | 0                                      | 0  |
| Not completed                                 | 143                                    | 127  |
| Adverse event, serious fatal                  | 1                                      | 1  |
| Protocol-Specified Withdrawal<br>Criteria Met | 1                                      | 3  |
| Physician decision                            | 4                                      | 3  |
| Consent withdrawn by subject                  | 12                                     | 6  |
| Adverse event, non-fatal                      | 11                                     | 3  |
| Reason Not Specified                          | -                                      | 3  |
| Non-Compliance With Study Drug                | -                                      | 1  |
| Study Terminated by Sponsor                   | 112                                    | 105  |
| Lost to follow-up                             | 2                                      | 2  |

## Baseline characteristics

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Prior Placebo to Bardoxolone Methyl |
|-----------------------|-------------------------------------|

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility urine albumin to creatinine ratio (UACR) >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

|                       |  |
|-----------------------|--|
| Reporting group title | Prior Bardoxolone Methyl to Bardoxolone Methyl |
|-----------------------|--|

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

| Reporting group values | Prior Placebo to Bardoxolone Methyl | Prior Bardoxolone Methyl to Bardoxolone Methyl | Total |
|------------------------|-------------------------------------|--|-------|
| Number of subjects     | 143                                 | 127  | 270   |
| Age Categorical        |                                     |  |       |
| Units: Subjects        |                                     |  |       |

|   |             |             |     |
|---|-------------|-------------|-----|
| Age continuous                            |             |             |     |
| Units: years                              |             |             |     |
| arithmetic mean                           | 48.8        | 48.3        |     |
| standard deviation                        | $\pm$ 13.26 | $\pm$ 13.82 | -   |
| Gender categorical                        |             |             |     |
| Units: Participants                       |             |             |     |
| Male                                      | 55          | 49          | 104 |
| Female                                    | 88          | 78          | 166 |
| Race                                      |             |             |     |
| Units: Subjects                           |             |             |     |
| American Indian or Alaska Native          | 2           | 0           | 2   |
| Asian                                     | 17          | 16          | 33  |
| Black or African American                 | 9           | 9           | 18  |
| Native Hawaiian or Other Pacific Islander | 0           | 1           | 1   |
| White                                     | 112         | 96          | 208 |

| Other               | 3   | 5   | 8   |
|---------------------|-----|-----|-----|
| Ethnicity           |     |     |     |
| Units: Subjects     |     |     |     |
| Hispanic/Latino     | 15  | 12  | 27  |
| Non-Hispanic/Latino | 128 | 115 | 243 |

## End points

### End points reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Prior Placebo to Bardoxolone Methyl |
|-----------------------|-------------------------------------|

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility urine albumin to creatinine ratio (UACR)  $>300$  milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR  $>300$  mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

|                       |  |
|-----------------------|--|
| Reporting group title | Prior Bardoxolone Methyl to Bardoxolone Methyl |
|-----------------------|--|

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility UACR  $>300$  mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR  $>300$  mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

### Primary: Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) <sup>[1]</sup> |
|-----------------|--|

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An SAE is any untoward medical occurrence that at any dose results in death, places the participant at immediate risk of death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or is a medically important event. AEs and SAEs that occurred within 30 days after the last dose were considered treatment-emergent. The study follow-up assessment was collected within 14 to 35 days after the last dose. The safety population included all participants who had received at least 1 dose of bardoxolone methyl in the 402-C-1803 study.

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

End point timeframe:

From the first dose of the study drug (baseline) up to the end of the study follow-up (up to 4.2 years)

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: Only descriptive analysis was planned to be analyzed.



| <b>End point values</b>     | Prior Placebo to<br>Bardoxolone<br>Methyl | Prior<br>Bardoxolone<br>Methyl to<br>Bardoxolone<br>Methyl |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group  |  |  |
| Number of subjects analysed | 143                                       | 127  |  |  |
| Units: participants         |   |  |  |  |
| AEs                         | 128                                       | 105  |  |  |
| SAEs                        | 12  | 20   |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of the study drug (baseline) up to the end of the study follow-up (up to 4.2 years)

Adverse event reporting additional description:

The safety population included all participants who had received at least 1 dose of bardoxolone methyl in the 402-C-1803 study.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Prior Placebo to Bardoxolone Methyl |
|-----------------------|-------------------------------------|

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose- escalation to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

|                       |  |
|-----------------------|--|
| Reporting group title | Prior Bardoxolone Methyl to Bardoxolone Methyl |
|-----------------------|--|

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14  $\pm$  3), and to 20 mg at Week 4 (Day 28  $\pm$  3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42  $\pm$  3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

| Serious adverse events  | Prior Placebo to Bardoxolone Methyl | Prior Bardoxolone Methyl to Bardoxolone Methyl |  |
|---|-------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                     |  |  |
| subjects affected / exposed   | 12 / 143 (8.39%)                    | 20 / 127 (15.75%)                              |  |
| number of deaths (all causes)                                       | 1                                   | 1  |  |
| number of deaths resulting from adverse events                      | 1                                   | 1  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |  |  |
| Uterine leiomyoma   |                                     |  |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Invasive ductal breast carcinoma                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Breast cancer  |                 |                 |  |
| subjects affected / exposed                          | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Hypertension   |                 |                 |  |
| subjects affected / exposed                          | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 143 (0.70%) | 0 / 127 (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 |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Portal vein thrombosis                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Endometrial hyperplasia                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Biopsy kidney                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Splenic rupture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebellar stroke                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic encephalopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid hemorrhage                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Pancytopenia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Blindness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Colitis ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholangitis acute                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (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                     |                 |                 |  |
| End stage renal disease                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic kidney disease                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Rotator cuff syndrome                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Gangrene  |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial pyelonephritis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 143 (0.70%) | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 143 (0.00%) | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                         | Prior Placebo to Bardoxolone Methyl | Prior Bardoxolone Methyl to Bardoxolone Methyl |  |
|---|-------------------------------------|--|--|
| Total subjects affected by non-serious adverse events     |                                     |  |  |
| subjects affected / exposed                               | 127 / 143 (88.81%)                  | 104 / 127 (81.89%)                             |  |
| Investigations  |                                     |  |  |
| Aspartate aminotransferase increased                      |                                     |  |  |
| subjects affected / exposed                               | 24 / 143 (16.78%)                   | 7 / 127 (5.51%)                                |  |
| occurrences (all)   | 26                                  | 7  |  |
| Alanine aminotransferase increased                        |                                     |  |  |
| subjects affected / exposed                               | 37 / 143 (25.87%)                   | 8 / 127 (6.30%)                                |  |
| occurrences (all)   | 38                                  | 9  |  |
| Blood creatinine increased                                |                                     |  |  |
| subjects affected / exposed                               | 3 / 143 (2.10%)                     | 7 / 127 (5.51%)                                |  |
| occurrences (all)   | 3                                   | 7  |  |
| Brain natriuretic peptide increased                       |                                     |  |  |
| subjects affected / exposed                               | 11 / 143 (7.69%)                    | 5 / 127 (3.94%)                                |  |
| occurrences (all)   | 18                                  | 12   |  |
| Gamma-glutamyltransferase increased                       |                                     |  |  |
| subjects affected / exposed                               | 11 / 143 (7.69%)                    | 0 / 127 (0.00%)                                |  |
| occurrences (all)   | 14                                  | 0  |  |
| N-terminal prohormone brain natriuretic peptide increased |                                     |  |  |
| subjects affected / exposed                               | 13 / 143 (9.09%)                    | 11 / 127 (8.66%)                               |  |
| occurrences (all)   | 18                                  | 13   |  |
| Vascular disorders  |                                     |  |  |



|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 8 / 143 (5.59%)<br>8    | 9 / 127 (7.09%)<br>9    |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 16 / 143 (11.19%)<br>29 | 9 / 127 (7.09%)<br>10   |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 5 / 143 (3.50%)<br>6    | 7 / 127 (5.51%)<br>7    |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                              | 9 / 143 (6.29%)<br>9    | 6 / 127 (4.72%)<br>6    |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 10 / 143 (6.99%)<br>11  | 11 / 127 (8.66%)<br>15  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 7 / 143 (4.90%)<br>9    | 7 / 127 (5.51%)<br>8    |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 14 / 143 (9.79%)<br>15  | 8 / 127 (6.30%)<br>10   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                      | 16 / 143 (11.19%)<br>20 | 8 / 127 (6.30%)<br>8    |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 9 / 143 (6.29%)<br>11   | 5 / 127 (3.94%)<br>6    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 12 / 143 (8.39%)<br>12  | 13 / 127 (10.24%)<br>16 |  |
| Respiratory, thoracic and mediastinal<br>disorders   |                         |                         |  |

|   |   |  |  |
|---|---|--|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 4 / 143 (2.80%)<br>4  | 11 / 127 (8.66%)<br>13   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | <br>12 / 143 (8.39%)<br>15<br><br>57 / 143 (39.86%)<br>96<br><br>4 / 143 (2.80%)<br>6   | <br>12 / 127 (9.45%)<br>13<br><br>45 / 127 (35.43%)<br>75<br><br>7 / 127 (5.51%)<br>10   |  |
| Infections and infestations<br>Sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Corona virus infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | <br>5 / 143 (3.50%)<br>5<br><br>22 / 143 (15.38%)<br>23<br><br>5 / 143 (3.50%)<br>8<br><br>12 / 143 (8.39%)<br>13<br><br>8 / 143 (5.59%)<br>9 | <br>8 / 127 (6.30%)<br>9<br><br>27 / 127 (21.26%)<br>27<br><br>8 / 127 (6.30%)<br>11<br><br>12 / 127 (9.45%)<br>15<br><br>12 / 127 (9.45%)<br>22 |  |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)  | <br>10 / 143 (6.99%)<br>10<br><br>10 / 143 (6.99%)<br>11  | <br>11 / 127 (8.66%)<br>14<br><br>4 / 127 (3.15%)<br>5   |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 30 January 2019  | <ol style="list-style-type: none"><li>1. Defined qualifying clinical study, as CARDINAL (2016-004395-22).</li><li>2. Clarified intent to measure B-type natriuretic peptide (BNP) and N-Terminal prohormone B-type natriuretic peptide (NT-Pro BNP) levels.</li></ol>   |
| 30 June 2020     | <ol style="list-style-type: none"><li>1. Added FALCON (2018-004651-20) as another qualifying study to enroll in EAGLE.</li><li>2. Updated for clarification regarding recording of AEs between prior qualifying study and Day 1 of EAGLE.</li><li>3. Updated text to include results of physical examinations as a safety parameter.</li><li>4. Updated section to manage transaminases (ALT/AST) elevations.</li><li>5. Updated information for resuming drug therapy after temporary discontinuation due to elevated liver enzymes.</li><li>6. Updated inclusion and exclusion criteria.</li><li>7. COVID-19 Mitigation Appendix was added to describe protocol modifications due to the pandemic.</li><li>8. Added section for participants reaching end stage kidney disease.</li></ol>   |
| 08 November 2022 | <ol style="list-style-type: none"><li>1. Lipid panel and Tanner Staging added to study visits.</li><li>2. Defined the qualifying study lab assessments which may be used for eligibility due to the variability of the off treatment follow-up schedule for studies 402-C-1603 (2016-004395-22)/402-C-1808 (2018-004651-20) protocol v5 and older vs. 402-C-1808 (2018-004651-20) protocol v6 and newer.</li><li>3. Differentiated between dose-titration period for adolescent participants enrolling from study 402-C-1603 (2016-004395-22) versus adolescent and adult participants enrolling from study 402-C-1808 (2018-004651-20).</li><li>4. Aligned with specific criteria and communication requirements added to study 402-C-1808 (2018-004651-20) protocol v6 related to the weight loss of adolescent and adult patients in the study to monitor for safety.</li><li>5. Simplified the instructions provided to investigators in the event of an increase in urinary albumin to creatinine ratios and to clarify that proteinuria is not required to be associated with other concurrent signs to consult with the medical monitor.</li></ol> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Early termination of trial due to discontinuation of all bardoxolone chronic kidney disease programs.

Notes: