



## Clinical trial results:

### A STUDY OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2016-000196-24    |
| Trial protocol           | ES DE BE NL CZ GB |
| Global end of trial date | 07 May 2020       |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 10 July 2021 |
| First version publication date | 10 July 2021 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 402-C-1504 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02657356 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                                     |
|------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Reata Pharmaceuticals, Inc.                                                                                         |
| Sponsor organisation address | 5320 Legacy Drive, Plano, United States, 75024                                                                      |
| Public contact               | Clinical Study Manager, Reata Pharmaceuticals, Inc., 1 972 865-2219, RegistroEspanolDeEstudiosClinicos@druginfo.com |
| Scientific contact           | Clinical Study Manager, Reata Pharmaceuticals, Inc., 1 972 865-2219, RegistroEspanolDeEstudiosClinicos@druginfo.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                       | 07 May 2020 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 07 May 2020 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 07 May 2020 |
| Was the trial ended prematurely?                     | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of bardoxolone methyl relative to placebo.

Protection of trial subjects:

IDMC reviewed unblinded safety data throughout the study and made recommendations regarding study continuation, modification or termination as appropriate to protect patient safety.

Background therapy:

Bardoxolone methyl or placebo was administered orally once a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 04 October 2016 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | 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: 6        |
| Country: Number of subjects enrolled | United States: 80 |
| Country: Number of subjects enrolled | Austria: 15       |
| Country: Number of subjects enrolled | Brazil: 9         |
| Country: Number of subjects enrolled | Argentina: 26     |
| Country: Number of subjects enrolled | Canada: 10        |
| Country: Number of subjects enrolled | Israel: 4         |
| Country: Number of subjects enrolled | Japan: 16         |
| Country: Number of subjects enrolled | Mexico: 12        |
| Country: Number of subjects enrolled | Philippines: 5    |
| Worldwide total number of subjects   | 202               |
| EEA total number of subjects         | 37                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 134 |
| From 65 to 84 years                       | 68  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Recruited patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH).

### Pre-assignment

Screening details:

Qualified patients with WHO Group I CTD-PAH were screened and enrolled per protocol inclusion/exclusion criteria.

### Period 1

|                              |                                                        |
|------------------------------|--------------------------------------------------------|
| Period 1 title               | Overall Trial (overall period)                         |
| Is this the baseline period? | Yes                                                    |
| Allocation method            | Randomised - controlled                                |
| Blinding used                | Double blind                                           |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

All patients, investigators, site personnel, laboratories, and central readers with direct involvement in the conduct of the study or their designees were blinded to treatment assignments throughout the trial. To maintain the blind, An IWRS system managed treatment assignments and distributed blinded study drug treatment kits. Investigators and patients were not blinded to dose level, but were be blinded to treatment assignment.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Placebo capsules |

Arm description:

Placebo capsules administered orally once a day for 24 weeks.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Placebo          |
| Investigational medicinal product name | Placebo Capsules |
| Investigational medicinal product code | Placebo          |
| Other name                             | Placebo          |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Placebo administered orally once a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Bardoxolone methyl capsules |
|------------------|-----------------------------|

Arm description:

Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4

|                                        |                                                                                                                                               |
|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Arm type                               | Experimental                                                                                                                                  |
| Investigational medicinal product name | Bardoxolone methyl capsules                                                                                                                   |
| 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 a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

| <b>Number of subjects in period 1</b>       | Placebo capsules | Bardoxolone methyl capsules |
|---------------------------------------------|------------------|-----------------------------|
| Started                                     | 102              | 100                         |
| Completed                                   | 90               | 93                          |
| Not completed                               | 12               | 7                           |
| Adverse event, not serious                  | 5                | 6                           |
| Consent withdrawn by subject                | 1                | 1                           |
| Study terminated by Sponsor                 | 5                | -                           |
| Protocol-specified withdrawal criterion met | 1                | -                           |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                          |                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                    | Placebo capsules            |
| Reporting group description:<br>Placebo capsules administered orally once a day for 24 weeks.                                                                            |                             |
| Reporting group title                                                                                                                                                    | Bardoxolone methyl capsules |
| Reporting group description:<br>Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4 |                             |

| Reporting group values             | Placebo capsules | Bardoxolone methyl capsules | Total |
|------------------------------------|------------------|-----------------------------|-------|
| Number of subjects                 | 102              | 100                         | 202   |
| Age categorical<br>Units: Subjects |                  |                             |       |

|                                                                         |                 |               |     |
|-------------------------------------------------------------------------|-----------------|---------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 56.5<br>± 13.17 | 55<br>± 13.57 | -   |
| Gender categorical<br>Units: Subjects                                   |                 |               |     |
| Female                                                                  | 91              | 88            | 179 |
| Male                                                                    | 11              | 12            | 23  |

### Subject analysis sets

|                                                                                                                                                                                                                                        |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Subject analysis set title                                                                                                                                                                                                             | Intent-to-treat population |
| Subject analysis set type                                                                                                                                                                                                              | Intention-to-treat         |
| Subject analysis set description:<br>All randomized patients categorized by their assigned treatment group regardless of treatment exposure. Analyses of both the primary and secondary efficacy outcomes will use the ITT population. |                            |
| Subject analysis set title                                                                                                                                                                                                             | Safety Population          |
| Subject analysis set type                                                                                                                                                                                                              | Safety analysis            |
| Subject analysis set description:<br>All patients who received at least one dose of randomized study drug.                                                                                                                             |                            |

| Reporting group values             | Intent-to-treat population | Safety Population |  |
|------------------------------------|----------------------------|-------------------|--|
| Number of subjects                 | 202                        | 202               |  |
| Age categorical<br>Units: Subjects |                            |                   |  |

|                                                                         |                 |   |  |
|-------------------------------------------------------------------------|-----------------|---|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 55.7<br>± 13.36 | ± |  |
|-------------------------------------------------------------------------|-----------------|---|--|

|                    |     |  |  |
|--------------------|-----|--|--|
| Gender categorical |     |  |  |
| Units: Subjects    |     |  |  |
| Female             | 179 |  |  |
| Male               | 23  |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                        |                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                                                                                  | Placebo capsules            |
| Reporting group description:<br>Placebo capsules administered orally once a day for 24 weeks.                                                                                                                                          |                             |
| Reporting group title                                                                                                                                                                                                                  | Bardoxolone methyl capsules |
| Reporting group description:<br>Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4                                                               |                             |
| Subject analysis set title                                                                                                                                                                                                             | Intent-to-treat population  |
| Subject analysis set type                                                                                                                                                                                                              | Intention-to-treat          |
| Subject analysis set description:<br>All randomized patients categorized by their assigned treatment group regardless of treatment exposure. Analyses of both the primary and secondary efficacy outcomes will use the ITT population. |                             |
| Subject analysis set title                                                                                                                                                                                                             | Safety Population           |
| Subject analysis set type                                                                                                                                                                                                              | Safety analysis             |
| Subject analysis set description:<br>All patients who received at least one dose of randomized study drug.                                                                                                                             |                             |

### Primary: Change from baseline in six-minute-walk distance (6MWD)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Change from baseline in six-minute-walk distance (6MWD) |
| End point description:<br>The 6MWT is a core clinical measure in the management of PAH and has been used as the primary endpoint in most previous registrational studies for PAH therapy. This unencouraged hallway walking test evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. |                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Primary                                                 |
| End point timeframe:<br>24 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                         |

| End point values                    | Placebo capsules   | Bardoxolone methyl capsules |  |  |
|-------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group             |  |  |
| Number of subjects analysed         | 102 <sup>[1]</sup> | 100 <sup>[2]</sup>          |  |  |
| Units: Meters                       |                    |                             |  |  |
| least squares mean (standard error) | 9.25 (± 4.954)     | -3.61 (± 4.952)             |  |  |

Notes:

[1] - Placebo capsules administered orally once a day for 24 weeks.

[2] - Bardoxolone methyl capsules administered orally once a day for 24 weeks.

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                         |                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                              | Change from baseline in 6MWT at Week 24 |
| Statistical analysis description:<br>A mixed model was fit with this outcome using Screening 6MWT, number of background PAH medications, and Day 1 hemoglobin as covariates, treatment group and visit as fixed factors, as well as the interaction of treatment group and visit, and Screening 6MWT and visit. Missing values were not |                                         |

imputed.

|                                         |                                                |
|-----------------------------------------|------------------------------------------------|
| Comparison groups                       | Placebo capsules v Bardoxolone methyl capsules |
| Number of subjects included in analysis | 202                                            |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.0683 <sup>[3]</sup>                        |
| Method                                  | Mixed models analysis                          |
| Parameter estimate                      | Mean difference (net)                          |
| Point estimate                          | -12.86                                         |
| Confidence interval                     |                                                |
| level                                   | 95 %                                           |
| sides                                   | 2-sided                                        |
| lower limit                             | -26.69                                         |
| upper limit                             | 0.98                                           |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 7.012                                          |

Notes:

[3] - Primary efficacy analysis compares changes from baseline (6WMT) between patients on  $\mu$  BARD to patients on  $\mu$  placebo at the wk 24 visit according to: Null hypothesis,  $H_0: (\mu \text{ BARD}) - (\mu \text{ placebo}) = 0m$ ; Alternative hypothesis  $H_1: (\mu \text{ BARD}) - (\mu \text{ placebo}) \neq 0 m$

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time administration of the first dose at the Day 1 visit until the final visit.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Bardoxolone methyl capsules |
|-----------------------|-----------------------------|

Reporting group description:

Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo capsules administered orally once a day for 24 weeks

| Serious adverse events                                              | Bardoxolone methyl capsules | Placebo           |  |
|---------------------------------------------------------------------|-----------------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                             |                   |  |
| subjects affected / exposed                                         | 16 / 100 (16.00%)           | 18 / 102 (17.65%) |  |
| number of deaths (all causes)                                       | 1                           | 1                 |  |
| number of deaths resulting from adverse events                      | 0                           | 1                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                   |  |
| Lung neoplasm malignant                                             |                             |                   |  |
| subjects affected / exposed                                         | 1 / 100 (1.00%)             | 0 / 102 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                       | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0             |  |
| Metastases to liver                                                 |                             |                   |  |
| subjects affected / exposed                                         | 1 / 100 (1.00%)             | 0 / 102 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                       | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0             |  |
| Breast cancer                                                       |                             |                   |  |
| subjects affected / exposed                                         | 0 / 100 (0.00%)             | 2 / 102 (1.96%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 2             |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0             |  |
| Cardiac disorders                                                   |                             |                   |  |
| Cardiac failure acute                                               |                             |                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                           |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Right ventricular failure                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Arteriospasm coronary                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                       |                 |                 |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                             |                 |                 |  |
| Syncope                                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Migraine                                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Chest pain                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Food poisoning                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal hypomotility                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proctitis ulcerative                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| 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 |                 |                 |  |
| Pulmonary arterial hypertension                 |                 |                 |  |
| subjects affected / exposed                     | 4 / 100 (4.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Nephritis                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 100 (2.00%) | 3 / 102 (2.94%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis infective                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 102 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis streptococcal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia viral                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 102 (0.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | Bardoxolone methyl capsules | Placebo           |  |
|---------------------------------------------------------------------|-----------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events               |                             |                   |  |
| subjects affected / exposed                                         | 91 / 100 (91.00%)           | 85 / 102 (83.33%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                   |  |
| Headache                                                            |                             |                   |  |
| subjects affected / exposed                                         | 14 / 100 (14.00%)           | 21 / 102 (20.59%) |  |
| occurrences (all)                                                   | 15                          | 28                |  |
| General disorders and administration site conditions                |                             |                   |  |
| Fatigue                                                             |                             |                   |  |
| subjects affected / exposed                                         | 9 / 100 (9.00%)             | 13 / 102 (12.75%) |  |
| occurrences (all)                                                   | 9                           | 13                |  |
| Oedema peripheral                                                   |                             |                   |  |
| subjects affected / exposed                                         | 9 / 100 (9.00%)             | 12 / 102 (11.76%) |  |
| occurrences (all)                                                   | 9                           | 14                |  |
| Non-cardiac chest pain                                              |                             |                   |  |

|                                                                         |                      |                         |  |
|-------------------------------------------------------------------------|----------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                        | 3 / 100 (3.00%)<br>3 | 6 / 102 (5.88%)<br>7    |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)             | 3 / 100 (3.00%)<br>3 | 3 / 102 (2.94%)<br>3    |  |
| Respiratory, thoracic and mediastinal disorders                         |                      |                         |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)            | 9 / 100 (9.00%)<br>9 | 12 / 102 (11.76%)<br>12 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)               | 6 / 100 (6.00%)<br>6 | 10 / 102 (9.80%)<br>12  |  |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all) | 4 / 100 (4.00%)<br>4 | 3 / 102 (2.94%)<br>3    |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)           | 4 / 100 (4.00%)<br>4 | 1 / 102 (0.98%)<br>1    |  |
| Rales<br>subjects affected / exposed<br>occurrences (all)               | 3 / 100 (3.00%)<br>3 | 3 / 102 (2.94%)<br>4    |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)    | 2 / 100 (2.00%)<br>2 | 3 / 102 (2.94%)<br>3    |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1 | 6 / 102 (5.88%)<br>6    |  |
| Psychiatric disorders                                                   |                      |                         |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)            | 3 / 100 (3.00%)<br>3 | 6 / 102 (5.88%)<br>6    |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)          | 1 / 100 (1.00%)<br>1 | 3 / 102 (2.94%)<br>3    |  |
| Investigations                                                          |                      |                         |  |

|                                                           |                 |                   |  |
|-----------------------------------------------------------|-----------------|-------------------|--|
| Gamma-glutamyltransferase increased                       |                 |                   |  |
| subjects affected / exposed                               | 8 / 100 (8.00%) | 2 / 102 (1.96%)   |  |
| occurrences (all)                                         | 8               | 2                 |  |
| Weight decreased                                          |                 |                   |  |
| subjects affected / exposed                               | 7 / 100 (7.00%) | 2 / 102 (1.96%)   |  |
| occurrences (all)                                         | 7               | 2                 |  |
| Aspartate aminotransferase increased                      |                 |                   |  |
| subjects affected / exposed                               | 6 / 100 (6.00%) | 1 / 102 (0.98%)   |  |
| occurrences (all)                                         | 6               | 1                 |  |
| Alanine aminotransferase increased                        |                 |                   |  |
| subjects affected / exposed                               | 6 / 100 (6.00%) | 0 / 102 (0.00%)   |  |
| occurrences (all)                                         | 6               | 0                 |  |
| N-terminal prohormone brain natriuretic peptide increased |                 |                   |  |
| subjects affected / exposed                               | 5 / 100 (5.00%) | 1 / 102 (0.98%)   |  |
| occurrences (all)                                         | 5               | 1                 |  |
| Brain natriuretic peptide increased                       |                 |                   |  |
| subjects affected / exposed                               | 3 / 100 (3.00%) | 2 / 102 (1.96%)   |  |
| occurrences (all)                                         | 3               | 2                 |  |
| Injury, poisoning and procedural complications            |                 |                   |  |
| Fall                                                      |                 |                   |  |
| subjects affected / exposed                               | 3 / 100 (3.00%) | 1 / 102 (0.98%)   |  |
| occurrences (all)                                         | 3               | 1                 |  |
| Cardiac disorders                                         |                 |                   |  |
| Palpitations                                              |                 |                   |  |
| subjects affected / exposed                               | 3 / 100 (3.00%) | 2 / 102 (1.96%)   |  |
| occurrences (all)                                         | 3               | 2                 |  |
| Nervous system disorders                                  |                 |                   |  |
| Dizziness                                                 |                 |                   |  |
| subjects affected / exposed                               | 8 / 100 (8.00%) | 12 / 102 (11.76%) |  |
| occurrences (all)                                         | 10              | 12                |  |
| Presyncope                                                |                 |                   |  |
| subjects affected / exposed                               | 3 / 100 (3.00%) | 1 / 102 (0.98%)   |  |
| occurrences (all)                                         | 4               | 1                 |  |
| Dizziness postural                                        |                 |                   |  |

|                                                                                                                     |                         |                         |  |
|---------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                    | 0 / 100 (0.00%)<br>0    | 3 / 102 (2.94%)<br>3    |  |
| Blood and lymphatic system disorders<br>Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all) | 6 / 100 (6.00%)<br>6    | 2 / 102 (1.96%)<br>2    |  |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 100 (1.00%)<br>1    | 3 / 102 (2.94%)<br>3    |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                         | 13 / 100 (13.00%)<br>15 | 21 / 102 (20.59%)<br>25 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                          | 12 / 100 (12.00%)<br>12 | 11 / 102 (10.78%)<br>13 |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                                | 9 / 100 (9.00%)<br>10   | 4 / 102 (3.92%)<br>4    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                        | 8 / 100 (8.00%)<br>8    | 7 / 102 (6.86%)<br>8    |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                    | 5 / 100 (5.00%)<br>5    | 6 / 102 (5.88%)<br>6    |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                                  | 3 / 100 (3.00%)<br>3    | 3 / 102 (2.94%)<br>3    |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)                                            | 3 / 100 (3.00%)<br>3    | 1 / 102 (0.98%)<br>1    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                            | 3 / 100 (3.00%)<br>3    | 1 / 102 (0.98%)<br>1    |  |
| Dyspepsia                                                                                                           |                         |                         |  |

|                                                                                                                      |                         |                         |  |
|----------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                     | 3 / 100 (3.00%)<br>3    | 1 / 102 (0.98%)<br>1    |  |
| Abdominal tenderness<br>subjects affected / exposed<br>occurrences (all)                                             | 3 / 100 (3.00%)<br>3    | 0 / 102 (0.00%)<br>0    |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                                                        | 3 / 100 (3.00%)<br>3    | 0 / 102 (0.00%)<br>0    |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                                                        | 0 / 100 (0.00%)<br>0    | 3 / 102 (2.94%)<br>3    |  |
| Skin and subcutaneous tissue disorders<br>Skin ulcer<br>subjects affected / exposed<br>occurrences (all)             | 3 / 100 (3.00%)<br>3    | 2 / 102 (1.96%)<br>2    |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 100 (1.00%)<br>1    | 3 / 102 (2.94%)<br>3    |  |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all) | 17 / 100 (17.00%)<br>19 | 6 / 102 (5.88%)<br>7    |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                        | 9 / 100 (9.00%)<br>10   | 7 / 102 (6.86%)<br>7    |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                                | 8 / 100 (8.00%)<br>9    | 2 / 102 (1.96%)<br>2    |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                          | 6 / 100 (6.00%)<br>6    | 5 / 102 (4.90%)<br>5    |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                       | 3 / 100 (3.00%)<br>5    | 12 / 102 (11.76%)<br>13 |  |
| Rheumatoid arthritis                                                                                                 |                         |                         |  |

|                                                                                          |                         |                         |  |
|------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                         | 1 / 100 (1.00%)<br>1    | 3 / 102 (2.94%)<br>5    |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 100 (0.00%)<br>0    | 3 / 102 (2.94%)<br>3    |  |
| Infections and infestations                                                              |                         |                         |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)    | 19 / 100 (19.00%)<br>27 | 11 / 102 (10.78%)<br>15 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                      | 11 / 100 (11.00%)<br>13 | 5 / 102 (4.90%)<br>5    |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)              | 8 / 100 (8.00%)<br>11   | 6 / 102 (5.88%)<br>11   |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                           | 7 / 100 (7.00%)<br>7    | 5 / 102 (4.90%)<br>5    |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                            | 4 / 100 (4.00%)<br>4    | 4 / 102 (3.92%)<br>4    |  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                      | 4 / 100 (4.00%)<br>4    | 2 / 102 (1.96%)<br>2    |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                            | 3 / 100 (3.00%)<br>3    | 3 / 102 (2.94%)<br>3    |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 100 (2.00%)<br>2    | 7 / 102 (6.86%)<br>7    |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 5 / 100 (5.00%)<br>5    | 1 / 102 (0.98%)<br>1    |  |
| Metabolism and nutrition disorders<br>Decreased appetite                                 |                         |                         |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 9 / 100 (9.00%) | 3 / 102 (2.94%) |  |
| occurrences (all)           | 9               | 3               |  |
| Gout                        |                 |                 |  |
| subjects affected / exposed | 5 / 100 (5.00%) | 0 / 102 (0.00%) |  |
| occurrences (all)           | 7               | 0               |  |
| Fluid retention             |                 |                 |  |
| subjects affected / exposed | 4 / 100 (4.00%) | 1 / 102 (0.98%) |  |
| occurrences (all)           | 6               | 1               |  |
| Hypokalaemia                |                 |                 |  |
| subjects affected / exposed | 4 / 100 (4.00%) | 1 / 102 (0.98%) |  |
| occurrences (all)           | 4               | 1               |  |
| Hypomagnesaemia             |                 |                 |  |
| subjects affected / exposed | 3 / 100 (3.00%) | 0 / 102 (0.00%) |  |
| occurrences (all)           | 3               | 0               |  |
| Musculoskeletal chest pain  |                 |                 |  |
| subjects affected / exposed | 4 / 100 (4.00%) | 2 / 102 (1.96%) |  |
| occurrences (all)           | 4               | 2               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 October 2016 | Version 2.0: Updated estimated study start and end dates, Clarified dose escalation and de-escalation rules, Updated Patient Inclusion Criteria (Criterion 7, 9, 10, 16, 21, and 30); Clarified Patient discontinuation criteria and management of fluid status; Added guidelines on Anemia treatment; Removed unnecessary excluded medication; Added guidelines for additional medications that may affect PAH walking distance and clarified the requirements for use of background medications for the treatment of CTD; Removed use of home health vendor; Clarification to consider potential comorbidities; Procedural clarification regarding the Assessment of Digital Ulcers; Clarification for patients not participating in PK sub-study; Clarification AE documentation to continue 28 days after last dose and made procedural reporting clarifications; Added Borg Dyspnea Scale appendix |

Notes:

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### 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.

In consideration of the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases, and on recommendation from the study's DSMB, the Sponsor concluded that continued exposure of these high-risk pa

Notes: