



## Clinical trial results:

### DP13 – A Phase II Study in Patients with Primary Aldosteronism to Evaluate the Efficacy, Safety and Tolerability of the Aldosterone Synthase Inhibitor, DP13, over an 8-week Treatment Period

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-000919-85 |
| Trial protocol           | NL IT          |
| Global end of trial date | 02 May 2022    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 21 December 2023 |
| First version publication date | 21 December 2023 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | DP13C201 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04007406 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | DAMIAN Pharma AG                                                                              |
| Sponsor organisation address | Haltli 6, Walchwil, Switzerland, 6318                                                         |
| Public contact               | Teresa Gerlock, DAMIAN Pharma AG, 041 0616010978, teresa.gerlock@damianpharma.com             |
| Scientific contact           | Christoph Schumacher, DAMIAN Pharma AG, 041 0616010978, christoph.schumacher@damianpharma.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                       | 11 January 2023 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 02 May 2022     |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 02 May 2022     |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

- To determine the efficacy of daily oral dexamethasone phosphate (DP13) treatment (all dose arms combined) to decrease the plasma aldosterone-to-renin ratio (ARR) from baseline in patients with primary aldosteronism (PA) following 8 weeks of treatment
- To determine the efficacy of daily oral dexamethasone phosphate (DP13) treatment (all dose arms combined) to reduce 24-hour ambulatory systolic blood pressure (aSBP) from baseline in patients with primary aldosteronism (PA) following 8 weeks of treatment

Protection of trial subjects:

The study was conducted in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonization (ICH)--Good Clinical Practice (GCP) Guidelines (ICH E6 (R2)), and all applicable laws and regulations.

Agreement to adhere to the protocol was established by Investigators signing and returning the protocol signature page.

Patient identities were kept confidential by assigning each patient a unique identifier consisting of a patient-specific numeric code, which was used throughout the study instead of the patient's name.

All study sites received the approval of the local Ethics Committee. Additionally, patients were treated to routine care by the site investigator/physician.

All patients were explained the nature and purpose of the study, the participation conditions and the risks and benefits to the patients before signing and dating the informed consent form.

Background therapy:

In order to prevent uncontrolled hypertension during the study, a fixed-dose regimen of doxazosin (1-8 mg QD), as first-line medication and, if necessary, verapamil slow release (40-120 mg BID) or diltiazem (slow release 90-360 mg daily) or amlodipine (2.5-10 mg QD) was implemented if clinically applicable 2 weeks prior to eligibility verification. Exceptionally, a calcium channel blocker could be used as first-line treatment if medically justified. Patients were not to take diagnosis-interfering medications as listed in the Endocrine Society Clinical Practice Guidelines (e.g., ACEi, ARB) for the duration of the study. Recently diagnosed patients on spironolactone were required to be washed out at least 8 weeks prior to study entry.

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 02 September 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 | Netherlands: 2 |
| Country: Number of subjects enrolled | Italy: 23      |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Switzerland: 10 |
| Worldwide total number of subjects   | 35              |
| EEA total number of subjects         | 25              |

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)                      | 35 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited as 'de novo' i.e., diagnosed with PA within 10 weeks of study entry or as 'recently diagnosed' i.e., diagnosed between 10 weeks and 1 year prior to study entry.

### Pre-assignment

Screening details:

Patient screening ARR and blood pressure were reviewed and approved by the Eligibility Review Panel prior to enrolling in the study.

A suppression test also needed to be performed prior to study entry to confirm diagnosis of PA. Patients underwent a 2-week placebo run-in prior to randomization.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 35 |
| Number of subjects completed | 35 |

### 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          |

Blinding implementation details:

IMP-containing jars were labeled/packed according to SOP based on the randomization list. The following controls were employed to maintain blinding:

1. Placebo capsules for the run-in period were identical in appearance to the DP13 capsules
2. The investigator and other members of staff involved in the study remained blinded to the treatment randomization code
3. Interim bioanalytical/hemodynamic data were provided to the central lab in a blinded manner

Emergency unblinding was possible

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | No       |
| Arm title                    | Baseline |

Arm description:

Prior to active treatment but following 2-weeks single-blind placebo run-in

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Arm type                                                  | No intervention  |
| No investigational medicinal product assigned in this arm |                  |
| Arm title                                                 | Active treatment |

Arm description:

Values after 8 weeks of dexamethasone phosphate treatment

|                                        |                         |
|----------------------------------------|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | dexamethasone phosphate |
| Investigational medicinal product code |                         |
| Other name                             | DP13                    |
| Pharmaceutical forms                   | Capsule                 |
| Routes of administration               | Oral use                |

Dosage and administration details:

Once daily, before meals

| <b>Number of subjects in period 1</b> | Baseline | Active treatment |
|---------------------------------------|----------|------------------|
| Started                               | 35       | 35               |
| Completed                             | 35       | 35               |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values                           | Overall trial | Total |  |
|--------------------------------------------------|---------------|-------|--|
| Number of subjects                               | 35            | 35    |  |
| Age categorical                                  |               |       |  |
| adults                                           |               |       |  |
| Units: Subjects                                  |               |       |  |
| Adults (18-64 years)                             | 35            | 35    |  |
| Age continuous                                   |               |       |  |
| Units: years                                     |               |       |  |
| arithmetic mean                                  | 52            |       |  |
| standard deviation                               | ± 9           | -     |  |
| Gender categorical                               |               |       |  |
| Units: Subjects                                  |               |       |  |
| Female                                           | 9             | 9     |  |
| Male                                             | 26            | 26    |  |
| Race                                             |               |       |  |
| Units: Subjects                                  |               |       |  |
| White                                            | 32            | 32    |  |
| Black or African American                        | 2             | 2     |  |
| Asian                                            | 1             | 1     |  |
| Body mass index                                  |               |       |  |
| Vital signs at baseline all dose groups combined |               |       |  |
| Units: kg/m2                                     |               |       |  |
| arithmetic mean                                  | 28            |       |  |
| standard deviation                               | ± 3.5         | -     |  |
| Office systolic blood pressure                   |               |       |  |
| Units: mm Hg                                     |               |       |  |
| arithmetic mean                                  | 148           |       |  |
| standard deviation                               | ± 12          | -     |  |
| Potassium                                        |               |       |  |
| Units: mmol/L                                    |               |       |  |
| arithmetic mean                                  | 3.5           |       |  |
| standard deviation                               | ± 0.4         | -     |  |
| Office diastolic blood pressure                  |               |       |  |
| Units: mm Hg                                     |               |       |  |
| arithmetic mean                                  | 92            |       |  |
| standard deviation                               | ± 10          | -     |  |
| 24-hour ambulatory systolic blood pressure       |               |       |  |
| Units: mm Hg                                     |               |       |  |
| arithmetic mean                                  | 143           |       |  |
| standard deviation                               | ± 14          | -     |  |
| Aldosterone-to-renin ratio                       |               |       |  |
| Units: ng*L/d?*mU                                |               |       |  |

|                                             |      |   |  |
|---------------------------------------------|------|---|--|
| arithmetic mean                             | 17.6 |   |  |
| standard deviation                          | ± 15 | - |  |
| 24-hour ambulatory diastolic blood pressure |      |   |  |
| Units: mm Hg                                |      |   |  |
| arithmetic mean                             | 88   |   |  |
| standard deviation                          | ± 8  | - |  |

### Subject analysis sets

|                                                                              |                       |
|------------------------------------------------------------------------------|-----------------------|
| Subject analysis set title                                                   | Baseline              |
| Subject analysis set type                                                    | Full analysis         |
| Subject analysis set description:                                            |                       |
| Baseline values after 2 weeks of placebo run-in                              |                       |
| Subject analysis set title                                                   | DP13 active treatment |
| Subject analysis set type                                                    | Full analysis         |
| Subject analysis set description:                                            |                       |
| Values following 8 weeks of once daily treatment with dexfadrostat phosphate |                       |

| Reporting group values                           | Baseline | DP13 active treatment |  |
|--------------------------------------------------|----------|-----------------------|--|
| Number of subjects                               | 35       | 35                    |  |
| Age categorical                                  |          |                       |  |
| adults                                           |          |                       |  |
| Units: Subjects                                  |          |                       |  |
| Adults (18-64 years)                             | 35       | 35                    |  |
| Age continuous                                   |          |                       |  |
| Units: years                                     |          |                       |  |
| arithmetic mean                                  | 52       | 52                    |  |
| standard deviation                               | ± 9      | ± 9                   |  |
| Gender categorical                               |          |                       |  |
| Units: Subjects                                  |          |                       |  |
| Female                                           | 9        | 9                     |  |
| Male                                             | 26       | 26                    |  |
| Race                                             |          |                       |  |
| Units: Subjects                                  |          |                       |  |
| White                                            | 32       | 32                    |  |
| Black or African American                        | 2        | 2                     |  |
| Asian                                            | 1        | 1                     |  |
| Body mass index                                  |          |                       |  |
| Vital signs at baseline all dose groups combined |          |                       |  |
| Units: kg/m2                                     |          |                       |  |
| arithmetic mean                                  | 28       | 28                    |  |
| standard deviation                               | ± 3.5    | ± 3.5                 |  |
| Office systolic blood pressure                   |          |                       |  |
| Units: mm Hg                                     |          |                       |  |
| arithmetic mean                                  | 148      | 148                   |  |
| standard deviation                               | ± 12     | ± 12                  |  |
| Potassium                                        |          |                       |  |
| Units: mmol/L                                    |          |                       |  |
| arithmetic mean                                  | 3.5      | 3.5                   |  |
| standard deviation                               | ± 0.4    | ± 0.4                 |  |

|                                                                                                      |              |              |  |
|------------------------------------------------------------------------------------------------------|--------------|--------------|--|
| Office diastolic blood pressure<br>Units: mm Hg<br>arithmetic mean<br>standard deviation             | 92<br>± 10   | 92<br>± 10   |  |
| 24-hour ambulatory systolic blood pressure<br>Units: mm Hg<br>arithmetic mean<br>standard deviation  | 143<br>± 14  | 143<br>± 14  |  |
| Aldosterone-to-renin ratio<br>Units: ng*L/d?*mU<br>arithmetic mean<br>standard deviation             | 17.6<br>± 15 | 17.6<br>± 15 |  |
| 24-hour ambulatory diastolic blood pressure<br>Units: mm Hg<br>arithmetic mean<br>standard deviation | 88<br>± 8    | 88<br>± 8    |  |



## End points

### End points reporting groups

|                                                                                                                    |                       |
|--------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                              | Baseline              |
| Reporting group description:<br>Prior to active treatment but following 2-weeks single-blind placebo run-in        |                       |
| Reporting group title                                                                                              | Active treatment      |
| Reporting group description:<br>Values after 8 weeks of dexamethasone phosphate treatment                          |                       |
| Subject analysis set title                                                                                         | Baseline              |
| Subject analysis set type                                                                                          | Full analysis         |
| Subject analysis set description:<br>Baseline values after 2 weeks of placebo run-in                               |                       |
| Subject analysis set title                                                                                         | DP13 active treatment |
| Subject analysis set type                                                                                          | Full analysis         |
| Subject analysis set description:<br>Values following 8 weeks of once daily treatment with dexamethasone phosphate |                       |

### Primary: 24-hour ambulatory systolic blood pressure (SBP)

|                                                                                                     |                                                  |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                     | 24-hour ambulatory systolic blood pressure (SBP) |
| End point description:                                                                              |                                                  |
| End point type                                                                                      | Primary                                          |
| End point timeframe:<br>Change from baseline to end of active treatment (8 weeks) in ambulatory SBP |                                                  |

| End point values                     | Baseline        | Active treatment | Baseline             | DP13 active treatment |
|--------------------------------------|-----------------|------------------|----------------------|-----------------------|
| Subject group type                   | Reporting group | Reporting group  | Subject analysis set | Subject analysis set  |
| Number of subjects analysed          | 35              | 35               | 35                   | 35                    |
| Units: mm Hg                         |                 |                  |                      |                       |
| arithmetic mean (standard deviation) | 143 (± 14)      | 132 (± 13)       | 143 (± 14)           | 132 (± 13)            |

### Statistical analyses

|                                                                                                                                                                                              |                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis title                                                                                                                                                                   | 24-hour ambulatory SBP           |
| Statistical analysis description:<br>Change in mean 24-hour ambulatory systolic blood pressure (SBP) from baseline to the end of the 8-week DP13 treatment period for all dose arms combined |                                  |
| Comparison groups                                                                                                                                                                            | Baseline v DP13 active treatment |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 70                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.05                         |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| Variability estimate                    | Standard deviation             |

### Primary: Aldosterone-to-renin ratio (ARR)

|                                                                                     |                                  |
|-------------------------------------------------------------------------------------|----------------------------------|
| End point title                                                                     | Aldosterone-to-renin ratio (ARR) |
| End point description:                                                              |                                  |
| End point type                                                                      | Primary                          |
| End point timeframe:                                                                |                                  |
| Change from baseline to end of active treatment (8 weeks), all dose groups combined |                                  |

| End point values                     | Baseline        | Active treatment |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 35              | 35               |  |  |
| Units: ng*L/dL*mU                    |                 |                  |  |  |
| arithmetic mean (standard deviation) | 17.6 (± 15)     | 2.2 (± 3.3)      |  |  |

### Statistical analyses

|                                                                                                              |                                  |
|--------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis title                                                                                   | Aldosterone-to-renin ratio (ARR) |
| Statistical analysis description:                                                                            |                                  |
| Change in plasma ARR from baseline to the end of the 8-week DP13 treatment period for all dose arms combined |                                  |
| Comparison groups                                                                                            | Active treatment v Baseline      |
| Number of subjects included in analysis                                                                      | 70                               |
| Analysis specification                                                                                       | Pre-specified                    |
| Analysis type                                                                                                | superiority                      |
| P-value                                                                                                      | < 0.05                           |
| Method                                                                                                       | ANOVA                            |
| Parameter estimate                                                                                           | Mean difference (final values)   |
| Confidence interval                                                                                          |                                  |
| level                                                                                                        | 95 %                             |
| sides                                                                                                        | 2-sided                          |
| Variability estimate                                                                                         | Standard deviation               |

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**Secondary: Potassium**

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|                 |           |
|-----------------|-----------|
| End point title | Potassium |
|-----------------|-----------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from baseline to end of active treatment (8 weeks)

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| End point values                     | Baseline        | Active treatment | Baseline             | DP13 active treatment |
|--------------------------------------|-----------------|------------------|----------------------|-----------------------|
| Subject group type                   | Reporting group | Reporting group  | Subject analysis set | Subject analysis set  |
| Number of subjects analysed          | 35              | 35               | 35                   | 35                    |
| Units: mmol/L                        |                 |                  |                      |                       |
| arithmetic mean (standard deviation) | 3.5 (± 0.4)     | 4.0 (± 0.3)      | 3.5 (± 0.4)          | 4.0 (± 0.3)           |

**Statistical analyses**

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | Plasma potassium |
|----------------------------|------------------|

Statistical analysis description:

Change in plasma potassium concentration from baseline to the end of the 8-week DP13 treatment period

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Baseline v DP13 active treatment |
|-------------------|----------------------------------|

|                                         |    |
|-----------------------------------------|----|
| Number of subjects included in analysis | 70 |
|-----------------------------------------|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |        |
|---------|--------|
| P-value | < 0.05 |
|---------|--------|

|        |                 |
|--------|-----------------|
| Method | t-test, 2-sided |
|--------|-----------------|

|                    |                                |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|                      |                    |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

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**Other pre-specified: 24-hour ambulatory diastolic blood pressure (aDBP)**

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|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | 24-hour ambulatory diastolic blood pressure (aDBP) |
|-----------------|----------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Change from baseline to the end of the 8-week DP13 treatment period, all dose groups combined

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| <b>End point values</b>              | Baseline        | Active treatment |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 35              | 35               |  |  |
| Units: mm Hg                         |                 |                  |  |  |
| arithmetic mean (standard deviation) | 88 (± 8)        | 82 (± 7)         |  |  |

## Statistical analyses

|                                                                                                   |                                                   |
|---------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                 | 4-hour ambulatory diastolic blood pressure (aDBP) |
| Statistical analysis description:                                                                 |                                                   |
| Change in mean 24-hour ambulatory DBP from baseline to the end of DP13 treatment period (8 weeks) |                                                   |
| Comparison groups                                                                                 | Baseline v Active treatment                       |
| Number of subjects included in analysis                                                           | 70                                                |
| Analysis specification                                                                            | Pre-specified                                     |
| Analysis type                                                                                     | superiority                                       |
| P-value                                                                                           | < 0.05                                            |
| Method                                                                                            | ANOVA                                             |
| Parameter estimate                                                                                | Mean difference (final values)                    |
| Confidence interval                                                                               |                                                   |
| level                                                                                             | 95 %                                              |
| sides                                                                                             | 2-sided                                           |
| Variability estimate                                                                              | Standard deviation                                |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected throughout the study including during the placebo run-in and withdrawal phases.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Safety analysis set |
|-----------------------|---------------------|

Reporting group description:

All randomized patients who received at least one dose of active study drug

| Serious adverse events                            | Safety analysis set |  |  |
|---------------------------------------------------|---------------------|--|--|
| Total subjects affected by serious adverse events |                     |  |  |
| subjects affected / exposed                       | 0 / 35 (0.00%)      |  |  |
| number of deaths (all causes)                     | 0                   |  |  |
| number of deaths resulting from adverse events    | 0                   |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events                            | Safety analysis set |  |  |
|-------------------------------------------------------|---------------------|--|--|
| Total subjects affected by non-serious adverse events |                     |  |  |
| subjects affected / exposed                           | 16 / 35 (45.71%)    |  |  |
| Investigations                                        |                     |  |  |
| Amylase increased                                     |                     |  |  |
| subjects affected / exposed                           | 1 / 35 (2.86%)      |  |  |
| occurrences (all)                                     | 1                   |  |  |
| Blood lactate dehydrogenase increased                 |                     |  |  |
| subjects affected / exposed                           | 1 / 35 (2.86%)      |  |  |
| occurrences (all)                                     | 1                   |  |  |
| Blood pressure diastolic increased                    |                     |  |  |
| subjects affected / exposed                           | 1 / 35 (2.86%)      |  |  |
| occurrences (all)                                     | 1                   |  |  |
| Blood pressure increased                              |                     |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                 |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                    | 1 / 35 (2.86%)<br>1                                                                                                             |  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                               | 1 / 35 (2.86%)<br>1                                                                                                             |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                            | 4 / 35 (11.43%)<br>4                                                                                                            |  |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                              | 2 / 35 (5.71%)<br>2                                                                                                             |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                          | 1 / 35 (2.86%)<br>1                                                                                                             |  |  |
| Gastrointestinal disorders<br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Dental caries<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Duodenitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastritis | 1 / 35 (2.86%)<br>1<br><br>1 / 35 (2.86%)<br>1<br><br>1 / 35 (2.86%)<br>1<br><br>2 / 35 (5.71%)<br>2<br><br>1 / 35 (2.86%)<br>1 |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Gastroesophageal reflux                         |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Nausea                                          |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Amenorrhoea                                     |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Breast tenderness                               |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Polymenorrhoea                                  |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough                                           |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Dyspnoea                                        |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Pruritus                                        |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Psychiatric disorders                           |                |  |  |
| Sleep disorder                                  |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Renal and urinary disorders                     |                |  |  |
| Cystitis                                        |                |  |  |

|                                                                                                    |                     |  |  |
|----------------------------------------------------------------------------------------------------|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                   | 1 / 35 (2.86%)<br>1 |  |  |
| Renal colic<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 35 (2.86%)<br>1 |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 35 (2.86%)<br>1 |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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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.

|      |
|------|
| None |
|------|

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36914591>