

**Clinical trial results:**

**A Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect on Urine Albumin-to-Creatinine Ratio (UACR), Pharmacodynamics, Safety, Tolerability and Pharmacokinetics of Multiple Oral Doses of MT-3995 as Add-on Therapy to ACE-I or ARB in Type II Diabetic Nephropathy Subjects with Albuminuria and an eGFR =>60 mL/min/1.73m<sup>2</sup>**

**Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002480-98 |
| Trial protocol           | HU LT SK BG    |
| Global end of trial date | 11 August 2014 |

**Results information**

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 June 2016 |
| First version publication date | 29 June 2016 |

**Trial information****Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | MT-3995-E06 |
|-----------------------|-------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01756703 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Mitsubishi Tanabe Pharma Corporation  |
| Sponsor organisation address | 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, Japan, 103-8405                             |
| Public contact               | General Information, Mitsubishi Tanabe Pharma Europe Ltd. , regulatory@mt-pharma-eu.com |
| Scientific contact           | General Information, Mitsubishi Tanabe Pharma Europe Ltd. , regulatory@mt-pharma-eu.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 October 2014 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 11 August 2014  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 11 August 2014  |
| Was the trial ended prematurely?                     | No              |

Notes:

### General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of multiple oral doses of MT-3995 in subjects with Type II diabetic kidney disease with protein in urine.

Protection of trial subjects:

Serum potassium algorithm  
AST/ALT liver function withdrawal criteria  
Serum creatinine withdrawal criteria

Background therapy:

- ACE-I or ARB treatment for at least 12 weeks prior to screening
- Stable dose of ACE-I or ARB from at least 4 weeks prior to screening until baseline visit and throughout the study period

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 28 November 2012 |
| 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 | Slovakia: 19  |
| Country: Number of subjects enrolled | Bulgaria: 9   |
| Country: Number of subjects enrolled | Hungary: 19   |
| Country: Number of subjects enrolled | Lithuania: 10 |
| Country: Number of subjects enrolled | Romania: 10   |
| Worldwide total number of subjects   | 67            |
| EEA total number of subjects         | 67            |

Notes:

#### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 54 |
| From 65 to 84 years                      | 13 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

67 subjects were randomised from 57 enrolling sites in Bulgaria, Hungary, Lithuania, Romania and Slovakia. FSS was 28/11/2012; LSS was 14/03/14. FSR was 11/03/2013; LSR was 24/04/2014. The study was conducted in university/public/private hospitals and specialised diabetes/renal impairment care practices.

### Pre-assignment

Screening details:

294 subjects were screened in order to randomise 67 subjects. The screening period for each subject was 2 weeks.

### 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 |

Blinding implementation details:

UACR and PK laboratory results were not distributed to the sites in order to prevent potential unblinding. MT-3995/placebo capsules appeared the same and same number of capsules were given.

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Group 1: Placebo oral capsules matching MT-3995 from Day 1 to the end of the treatment period (Week 8).

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

Dosage and administration details:

Placebo was matching the MT-3995 capsules in number and appearance.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | MT-3995 - 5 mg |
|------------------|----------------|

Arm description:

Group 2: 80 mg loading dose on Day 1 and 5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | MT-3995      |
| Investigational medicinal product code | MT-3995      |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

80 mg loading dose respectively on day 1 followed by 5 mg maintenance dose from Day 2 until end of treatment period (Week 8).

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | MT-3995 - 10 mg |
|------------------|-----------------|

Arm description:

Group 3: 160 mg loading dose on Day 1 and 10 mg od maintenance dose from Day 2 (Week 1) to the

end of the treatment period (Week 8).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | MT-3995      |
| Investigational medicinal product code | MT-3995      |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

160 mg loading dose respectively on day 1 followed by 10 mg maintenance dose od from Day 2 until end of treatment period (Week 8).

| <b>Number of subjects in period 1</b>         | Placebo | MT-3995 - 5 mg | MT-3995 - 10 mg |
|---|---------|----------------|-----------------|
| Started                                       | 22      | 23             | 22              |
| Completed                                     | 21      | 21             | 19              |
| Not completed                                 | 1       | 2              | 3               |
| Adverse event, non-fatal                      | -       | -              | 1               |
| Central serum potassium was high at baseline  | 1       | 1              | 2               |
| Central serum potassium WD criteria fulfilled | -       | 1              | -               |

## Baseline characteristics

### Reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Placebo         |
| Reporting group description:   |                 |
| Group 1: Placebo oral capsules matching MT-3995 from Day 1 to the end of the treatment period (Week 8).                              |                 |
| Reporting group title  | MT-3995 - 5 mg  |
| Reporting group description:   |                 |
| Group 2: 80 mg loading dose on Day 1 and 5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8).   |                 |
| Reporting group title  | MT-3995 - 10 mg |
| Reporting group description:   |                 |
| Group 3: 160 mg loading dose on Day 1 and 10 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8). |                 |

| Reporting group values                             | Placebo | MT-3995 - 5 mg | MT-3995 - 10 mg |
|--|---------|----------------|-----------------|
| Number of subjects                                 | 22      | 23             | 22              |
| Age categorical                                    |         |                |                 |
| Units: Subjects                                    |         |                |                 |
| In utero   | 0       | 0              | 0               |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0              | 0               |
| Newborns (0-27 days)                               | 0       | 0              | 0               |
| Infants and toddlers (28 days-23 months)           | 0       | 0              | 0               |
| Children (2-11 years)                              | 0       | 0              | 0               |
| Adolescents (12-17 years)                          | 0       | 0              | 0               |
| Adults (18-64 years)                               | 17      | 21             | 16              |
| From 65-84 years                                   | 5       | 2              | 6               |
| 85 years and over                                  | 0       | 0              | 0               |
| Age continuous                                     |         |                |                 |
| Units: years                                       |         |                |                 |
| arithmetic mean                                    | 56.4    | 56             | 58.2            |
| standard deviation                                 | ± 9.8   | ± 7.3          | ± 9.4           |
| Gender categorical                                 |         |                |                 |
| Units: Subjects                                    |         |                |                 |
| Female   | 9       | 3              | 6               |
| Male   | 13      | 20             | 16              |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 67    |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 0     |  |  |
| Children (2-11 years)                              | 0     |  |  |

|                           |    |  |  |
|---------------------------|----|--|--|
| Adolescents (12-17 years) | 0  |  |  |
| Adults (18-64 years)      | 54 |  |  |
| From 65-84 years          | 13 |  |  |
| 85 years and over         | 0  |  |  |
| Age continuous            |    |  |  |
| Units: years              |    |  |  |
| arithmetic mean           |    |  |  |
| standard deviation        | -  |  |  |
| Gender categorical        |    |  |  |
| Units: Subjects           |    |  |  |
| Female                    | 18 |  |  |
| Male                      | 49 |  |  |

## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Placebo         |
| Reporting group description:<br>Group 1: Placebo oral capsules matching MT-3995 from Day 1 to the end of the treatment period (Week 8).                              |                 |
| Reporting group title  | MT-3995 - 5 mg  |
| Reporting group description:<br>Group 2: 80 mg loading dose on Day 1 and 5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8).   |                 |
| Reporting group title  | MT-3995 - 10 mg |
| Reporting group description:<br>Group 3: 160 mg loading dose on Day 1 and 10 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8). |                 |

### Primary: Not Applicable - none reported as safety is primary endpoint

|  |   |
|--|---|
| End point title  | Not Applicable - none reported as safety is primary endpoint <sup>[1]</sup> |
| End point description:<br>No primary endpoints were defined for efficacy or PD variables. Safety was the primary endpoint. |   |
| End point type   | Primary   |
| End point timeframe:<br>Not applicable   |   |

Notes:

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

Justification: The primary endpoint was safety and the data are provided in the AE section.

| End point values            | Placebo          | MT-3995 - 5 mg   | MT-3995 - 10 mg  |  |
|-----------------------------|------------------|------------------|------------------|--|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  |  |
| Number of subjects analysed | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> | 0 <sup>[4]</sup> |  |
| Units: Not applicable       |                  |                  |                  |  |

Notes:

[2] - Not applicable as the primary endpoint was safety and the data are provided in the AE section.

[3] - Not applicable as the primary endpoint was safety and the data are provided in the AE section.

[4] - Not applicable as the primary endpoint was safety and the data are provided in the AE section.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Start of double-blind treatment to end of 8 week follow-up period. Treatment-Emergent AEs were defined as those which started or worsened in severity after the first dose of double-blind study medication.

Adverse event reporting additional description:

During the study visits regular questioning of each subject by study staff. No leading questions were asked. Data recorded under "Non Serious Adverse Events" also includes serious adverse events.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

### Reporting groups

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

Reporting group description:

Group 1: Placebo oral capsules matching MT-3995 from Day 1 to the end of the treatment period (Week 8).

|                       |               |
|-----------------------|---------------|
| Reporting group title | MT-3995 - 5mg |
|-----------------------|---------------|

Reporting group description:

Group 2: 80 mg loading dose on Day 1 and 5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8) and 8 week follow up.

|                       |                |
|-----------------------|----------------|
| Reporting group title | MT-3995 - 10mg |
|-----------------------|----------------|

Reporting group description:

Group 3: 160 mg loading dose on Day 1 and 10 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8) and 8 week follow up.

| <b>Serious adverse events</b>                     | Placebo        | MT-3995 - 5mg  | MT-3995 - 10mg |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 1 / 22 (4.55%) | 2 / 23 (8.70%) | 1 / 22 (4.55%) |
| number of deaths (all causes)                     | 0              | 1              | 0              |
| number of deaths resulting from adverse events    | 0              | 1              | 0              |
| Injury, poisoning and procedural complications    |                |                |                |
| Contusion   |                |                |                |
| subjects affected / exposed                       | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Nerve root injury lumbar                          |                |                |                |
| subjects affected / exposed                       | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Atrial Fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Chronic Obstructive Pulmonary Disease           |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypercapnia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Placebo         | MT-3995 - 5mg   | MT-3995 - 10mg  |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |
| subjects affected / exposed                           | 8 / 22 (36.36%) | 7 / 23 (30.43%) | 7 / 22 (31.82%) |
| Investigations  |                 |                 |                 |
| Electrocardiogram QT prolonged                        |                 |                 |                 |
| subjects affected / exposed                           | 2 / 22 (9.09%)  | 0 / 23 (0.00%)  | 0 / 22 (0.00%)  |
| occurrences (all)                                     | 2               | 0               | 0               |
| Amylase increased                                     |                 |                 |                 |
| subjects affected / exposed                           | 0 / 22 (0.00%)  | 0 / 23 (0.00%)  | 1 / 22 (4.55%)  |
| occurrences (all)                                     | 0               | 0               | 1               |
| Blood glucose increased                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 22 (0.00%)  | 1 / 23 (4.35%)  | 0 / 22 (0.00%)  |
| occurrences (all)                                     | 0               | 1               | 0               |
| Liver function test abnormal                          |                 |                 |                 |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)     | 0 / 22 (0.00%)<br>0 | 1 / 23 (4.35%)<br>1 | 0 / 22 (0.00%)<br>0 |
| Injury, poisoning and procedural complications       |                     |                     |                     |
| Accidental overdose                                  |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 1 / 23 (4.35%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 0                   | 1                   | 0                   |
| Contusion  |                     |                     |                     |
| subjects affected / exposed                          | 1 / 22 (4.55%)      | 0 / 23 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 1                   | 0                   | 0                   |
| Nerve root injury lumbar                             |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 1 / 23 (4.35%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 0                   | 1                   | 0                   |
| Cardiac disorders                                    |                     |                     |                     |
| Angina pectoris                                      |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 0 / 23 (0.00%)      | 1 / 22 (4.55%)      |
| occurrences (all)                                    | 0                   | 0                   | 1                   |
| Atrial fibrillation                                  |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 1 / 23 (4.35%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 0                   | 1                   | 0                   |
| Extrasystoles  |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 1 / 23 (4.35%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 0                   | 1                   | 0                   |
| Myocardial infarction                                |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 0 / 23 (0.00%)      | 1 / 22 (4.55%)      |
| occurrences (all)                                    | 0                   | 0                   | 1                   |
| Nervous system disorders                             |                     |                     |                     |
| Diabetic neuropathy                                  |                     |                     |                     |
| subjects affected / exposed                          | 0 / 22 (0.00%)      | 0 / 23 (0.00%)      | 1 / 22 (4.55%)      |
| occurrences (all)                                    | 0                   | 0                   | 1                   |
| Dizziness  |                     |                     |                     |
| subjects affected / exposed                          | 1 / 22 (4.55%)      | 0 / 23 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 1                   | 0                   | 0                   |
| General disorders and administration site conditions |                     |                     |                     |
| Oedema peripheral                                    |                     |                     |                     |
| subjects affected / exposed                          | 1 / 22 (4.55%)      | 0 / 23 (0.00%)      | 0 / 22 (0.00%)      |
| occurrences (all)                                    | 1                   | 0                   | 0                   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders                      |                |                |                |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                               | 1              | 0              | 1              |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 1 / 22 (4.55%) |
| occurrences (all)                               | 0              | 1              | 1              |
| Abdominal pain upper                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Gastrooesophageal reflux disease                |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Reproductive system and breast disorders        |                |                |                |
| Erectile dysfunction                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Chronic obstructive pulmonary disease           |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Hypercapnia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Infections and infestations                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cystitis                                |                |                |                |
| subjects affected / exposed             | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Gastroenteritis viral                   |                |                |                |
| subjects affected / exposed             | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Nasopharyngitis                         |                |                |                |
| subjects affected / exposed             | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Upper respiratory tract infection       |                |                |                |
| subjects affected / exposed             | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Urinary tract infection                 |                |                |                |
| subjects affected / exposed             | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Viral upper respiratory tract infection |                |                |                |
| subjects affected / exposed             | 1 / 22 (4.55%) | 0 / 23 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Metabolism and nutrition disorders      |                |                |                |
| Hyperglycaemia                          |                |                |                |
| subjects affected / exposed             | 1 / 22 (4.55%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 1              | 1              | 0              |
| Decreased appetite                      |                |                |                |
| subjects affected / exposed             | 0 / 22 (0.00%) | 0 / 23 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Hyperkalaemia                           |                |                |                |
| subjects affected / exposed             | 0 / 22 (0.00%) | 1 / 23 (4.35%) | 0 / 22 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 07 January 2014 | Reduced lower limit of UACR incl. crit. from 200 to 50 mg/g; lowering of eGRF incl. crit. from 60 to 57 mL/min/1.73m <sup>2</sup> ; incr. of > K+ incl. crit. from 5.0 to 5.2 mmol/L; error corr., further clarif. |
| 30 April 2014   | Former primary UACR objective now secondary objective and safety & tolerability now primary obj.; sample size modified accordingly   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported