



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 =>30-<60 mL/min/1.73m²

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-002481-12 |
| Trial protocol | HU CZ SK BG PL |
| Global end of trial date | 15 September 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-E07 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01756716 |
| 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 | 11 November 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 September 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 | 07 December 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 | Poland: 4 |
| Country: Number of subjects enrolled | Slovakia: 11 |
| Country: Number of subjects enrolled | Bulgaria: 9 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Romania: 5 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 49 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 27 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

49 subjects were randomised from 64 enrolling sites in Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia. FSS was 07/12/2012; LSS was 18/04/14. FSR was 14/02/2013; LSR was 20/06/2014.

The study was conducted in university/public/private hospitals and specialised diabetes/renal impairment care practices.

Pre-assignment

Screening details:

317 subjects were screened in order to randomise 49 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 |
| Arm title | 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.

| | |
|------------------|------------------|
| Arm title | MT-3995 - 2.5 mg |
|------------------|------------------|

Arm description:

Group 2: 40 mg loading dose on Day 1 and 2.5 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:

40 mg loading dose respectively on day 1 followed by 2.5 mg maintenance dose od from Day 2 until end of treatment period (Week 8).

| | |
|------------------|----------------|
| Arm title | MT-3995 - 5 mg |
|------------------|----------------|

Arm description:

Group 3: 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 od from Day 2 until end of treatment period (Week 8).

| Number of subjects in period 1 | Placebo | MT-3995 - 2.5 mg | MT-3995 - 5 mg |
|--|---------|------------------|----------------|
| Started | 16 | 17 | 16 |
| Completed | 14 | 14 | 14 |
| Not completed | 2 | 3 | 2 |
| Adverse event, not serious | 1 | - | - |
| Protocol specific reason | 1 | 1 | - |
| ACE-I dose increase during run-in | - | 1 | - |
| Central serum potassium was high at baseline | - | 1 | 2 |

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 - 2.5 mg |
| Reporting group description: | |
| Group 2: 40 mg loading dose on Day 1 and 2.5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8). | |
| Reporting group title | MT-3995 - 5 mg |
| Reporting group description: | |
| Group 3: 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 values | Placebo | MT-3995 - 2.5 mg | MT-3995 - 5 mg |
|--|---------|------------------|----------------|
| Number of subjects | 16 | 17 | 16 |
| 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) | 6 | 11 | 10 |
| From 65-84 years | 10 | 6 | 6 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.4 | 62.1 | 60.4 |
| standard deviation | ± 4.5 | ± 7.1 | ± 9.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 5 | 6 |
| Male | 11 | 12 | 10 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 49 | | |
| 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) | 27 | | |
| From 65-84 years | 22 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | | |
| Male | 33 | | |

End points

End points 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 - 2.5 mg |
| Reporting group description: Group 2: 40 mg loading dose on Day 1 and 2.5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8). | |
| Reporting group title | MT-3995 - 5 mg |
| Reporting group description: Group 3: 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). | |

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

| | |
|--|---|
| End point title | Not Applicable - none reported as safety is primary endpoint ^[1] |
| End point description: No primary endpoints were defined for efficacy or PD variables. Safety was the primary endpoint. | |
| End point type | Primary |
| End point timeframe: 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 - 2.5 mg | MT-3995 - 5 mg | |
|-----------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| 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 - 2.5 mg |
|-----------------------|------------------|

Reporting group description:

Group 2: 40 mg loading dose on Day 1 and 2.5 mg od maintenance dose from Day 2 (Week 1) to the end of the treatment period (Week 8).

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

Reporting group description:

Group 3: 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.

| Serious adverse events | Placebo | MT-3995 - 2.5 mg | MT-3995 - 5 mg |
|---|----------------|------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 1 / 16 (6.25%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 16 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | MT-3995 - 2.5 mg | MT-3995 - 5 mg |
|---|-----------------|------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | 5 / 17 (29.41%) | 3 / 16 (18.75%) |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arteriospasm coronary | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Left ventricular hypertrophy | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | 0 / 16 (0.00%) 0 |
| Myocardial ischaemia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 17 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 17 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | 0 / 16 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 17 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Gastrointestinal sounds abnormal subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 17 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Erythema | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Tendon pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 17 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | 0 / 16 (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 |
|-----------------|--|
| 10 October 2013 | Reduced lower limit of UACR incl. criteria from 200 to 50 mg/g; error correction; further clarifications. |
| 03 January 2014 | Widening of eGFR incl. criteria from 30-60 to 27-62 mL/min/1.73m ² ; increase of > serum potassium incl. criteria from 5.0 to 5.2 mmol/L; error correction, further clarifications. |
| 21 May 2014 | Former primary UACR objective now secondary objective and safety & tolerability now primary obj.; sample size modified accordingly. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported