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

subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	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 eGRF incl. criteria from 30-60 to 27-62 mL/min/1.73m2; 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