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/1.73m2

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 enrollinig 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
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 - 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).

Arm title	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).

Number of subjects in period 1	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 fullfilled	-	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:	
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).	

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 - 5 mg	MT-3995 - 10 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 - 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.

Serious adverse events	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 Fibrilation			
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 %

Non-serious adverse events	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	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	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/1.73m2; 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported