Clinical trial results:
A Phase IIa, Multi-Centre, Randomised, Double-Blind, Cross-Over, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of MT-8554 in Subjects with Painful Diabetic Peripheral Neuropathy Incorporating an Open Label Pilot Arm

Summary

EudraCT number	2016-002571-10
Trial protocol	HU PL DE
Global end of trial date	08 August 2018

Results information

Result version number	v1 (current)
This version publication date	18 August 2019
First version publication date	18 August 2019

Trial information

Trial identification

Sponsor protocol code	MT-8554-E06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03172598
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	08 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2018
Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1 (Pilot Arm):
To evaluate the safety and tolerability of MT-8554 to determine the dose level administered in Part 2.

Part 2 (Cross-over Arm):
To evaluate the efficacy of MT-8554 in reducing pain intensity in subjects with painful DPN.

Protection of trial subjects:

Subjects were withdrawn from the study if any of the following scenarios occurred:
• The subject wished to withdraw from further participation.
• The subject was significantly noncompliant with the Protocol.
• Continuing in the study would have been detrimental to the subject's safety in the opinion of the Investigator, e.g.,
- The subject experienced intolerable AEs or serious adverse events (SAEs)
- The subject became pregnant from the Screening Visit until 3 months after the last dose of IMP
- The subject had CS changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result
- The subject had an increase in QTcF to ≥500 ms or increase of ≥60 ms from baseline (pre-dose on Day 1), as confirmed with 3 consecutive ECGs taken at least 5 minutes apart in a 30-minute period
- Development of any CS liver dysfunction, as follows:
• ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, or
• ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or
• ALT or AST >5 × ULN
- The subject experienced signs or symptoms of significant hypothermia or a tympanic/oral body temperature <35°C over a 1 hour period (confirmed by repeat assessment performed at least 60 minutes after the original assessment).
In addition, a subject may have been withdrawn at any time for reason(s) other than those listed here.

Background therapy:

Prior and concomitant medications which were considered necessary for the safety and well-being of the subject were permitted during the study at the discretion of the Investigator, provided the medication was not listed within the exclusion criteria (Section 9.3.2) or the prohibited medications (Section 9.4.7.2). Every effort was made to keep subjects on stable concomitant medications.

Subjects were also permitted to use acetylsalicylic acid up to 325 mg/day post-myocardial infarction or prophylactically at doses ongoing at study entry for prevention of transient ischaemic attack, and zolpidem 5 mg for sleep disorders.

Acetaminophen/paracetamol was allowable as rescue medication if dosed at up to 3 g/day, if required for pain relief. Should acetaminophen/paracetamol have provided insufficient relief from pain then use of metamizole in single doses up to 1 g and up to the maximum daily dose of 4 g was allowed. The label restrictions for acetaminophen/paracetamol and metamizole applied.

Evidence for comparator: -

Actual start date of recruitment	25 July 2017
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: 36
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 13
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	39
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential study subjects were identified using a range of study-specific methods, as appropriate. Subjects were selected from those currently attending clinics for the treatment of DPN or identified from a review of relevant databases. All recruitment material was approved by an Independent Ethics Committee (IEC) prior to implementation.

Pre-assignment

Screening details:

Eligible subjects were required to complete a washout from any current DPN medications. For part 1, subjects received open label oral dose of MT-8554. For part 2, subjects attended a baseline visit at Day -7 and received a single-blind placebo for a period of a week before being randomised into double-blind cross over treatment sequence.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Part 1 MT-8554 20mg Open Label

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-8554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg BID

Arm title	Part 1 MT-8554 50mg Open Label

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-8554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50 mg BID

Arm title	Part 2 Overall

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-8554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: 20mg BID during one of two treatment periods.	
Investigational medicinal product name	MT-8554 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20mg BID during two baselines, washout and one of two treatment periods.

Number of subjects in period 1	Part 1 MT-8554 20mg Open Label	Part 1 MT-8554 50mg Open Label	Part 2 Overall
Started	5	4	52
Completed	4	2	34
Not completed	1	2	18
Consent withdrawn by subject	-	-	3
Adverse event, non-fatal	-	1	14
protocol specific reason	-	1	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 MT-8554 20mg Open Label
Reporting group description: -	
Reporting group title	Part 1 MT-8554 50mg Open Label
Reporting group description: -	
Reporting group title	Part 2 Overall
Reporting group description: -	

Reporting group values	Part 1 MT-8554 20mg Open Label	Part 1 MT-8554 50mg Open Label	Part 2 Overall
Number of subjects	5	4	52
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)	3	3	33
From 65-84 years	2	1	19
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.8	63.3	60.1
standard deviation	± 6.4	± 6.8	± 9.5
Gender categorical Units: Subjects			
Female	3	1	19
Male	2	3	33

Reporting group values	Total		
Number of subjects	61		
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)	39		
From 65-84 years	22		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	23		
Male	38		

End points

End points reporting groups

Reporting group title	Part 1 MT-8554 20mg Open Label
Reporting group description: -	
Reporting group title	Part 1 MT-8554 50mg Open Label
Reporting group description: -	
Reporting group title	Part 2 Overall
Reporting group description: -	
Subject analysis set title	Part 2 Placebo Week 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all randomised subjects who receive at least 1 dose of IMP and who have at least 1 post-baseline efficacy assessment.	
Subject analysis set title	Part 2 MT-8554 20mg week 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all randomised subjects who receive at least 1 dose of IMP and who have at least 1 post-baseline efficacy assessment.	
Subject analysis set title	Part 2 Placebo Week 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all randomised subjects who receive at least 1 dose of IMP and who have at least 1 post-baseline efficacy assessment.	
Subject analysis set title	Part 2 MT-8554 20mg week 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all randomised subjects who receive at least 1 dose of IMP and who have at least 1 post-baseline efficacy assessment.	

Primary: Change from baseline in the weekly median 24-hour API score

End point title	Change from baseline in the weekly median 24-hour API score
End point description:	
End point type	Primary
End point timeframe:	
week 1 and 2	

End point values	Part 2 Placebo Week 1	Part 2 MT-8554 20mg week 1	Part 2 Placebo Week 2	Part 2 MT-8554 20mg week 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	45	42	40
Units: no unit				
least squares mean (standard error)	-0.37 (± 0.18)	-0.67 (± 0.16)	-0.58 (± 0.20)	-0.95 (± 0.20)

Statistical analyses

Statistical analysis title	Change from Baseline Weekly API Score at week 1

Statistical analysis description:

The 'number of subjects included in analysis' is not correct because of the cross-over study design (subject analysis sets were not mutually exclusive). The 'number of subjects included in analysis' for the comparison is equivalent to the 'number of subjects analysed'.

Comparison groups	Part 2 Placebo Week 1 v Part 2 MT-8554 20mg week 1
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.202 [1]
Method	ANCOVA

Notes:

[1] - Difference MT-8554 20mg - Placebo

Statistical analysis title	Change from Baseline Weekly API Score at week 2

Statistical analysis description:

The 'number of subjects included in analysis' is not correct because of the cross-over study design (subject analysis sets were not mutually exclusive). The 'number of subjects included in analysis' for the comparison is equivalent to the 'number of subjects analysed'.

Comparison groups	Part 2 Placebo Week 2 v Part 2 MT-8554 20mg week 2
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155 [2]
Method	ANCOVA

Notes:

[2] - Difference MT-8554 20mg - Placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time written informed consent was obtained until the end of the Follow-up Period or the withdrawal of the subject from the study

Adverse event reporting additional description:

Part 1 reported all AEs and frequency threshold was only applied to part 2. Following AEs were reported in part1, but did not meet the 5% threshold in part 2: Headache, Peripheral sensory neuropathy, hot flush, dry skin, back pain. Due to the design of the database, these AEs were also reported for part 2 despite not meeting threshold.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Part 1 20mg MT-8554
Reporting group description: -	
Reporting group title	Part 1 50mg MT-8554
Reporting group description: -	
Reporting group title	Part 2 Placebo
Reporting group description: -	
Reporting group title	Part 2 MT-8554 20mg
Reporting group description: -	

Serious adverse events	Part 1 20mg MT-8554	Part 1 50mg MT-8554	Part 2 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2 MT-8554 20mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 52 (5.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1 20mg MT-8554	Part 1 50mg MT-8554	Part 2 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	4 / 4 (100.00%)	16 / 43 (37.21%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	2 / 43 (4.65%)
occurrences (all)	3	0	6
Hypoaesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Burning sensation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dizziness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	2 / 43 (4.65%)
occurrences (all)	1	1	4
Hypothermia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	4
Feeling cold			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Hypoaesthesia oral			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	7
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Paraesthesia oral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Skin burning sensation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 43 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 2 MT-8554 20mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 52 (75.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypoaesthesia			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	12		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	8		
Burning sensation			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	9		
Autonomic nervous system imbalance			

subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	15 / 52 (28.85%)		
occurrences (all)	85		
Hypothermia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Asthenia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	3		
Feeling cold			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Gastrointestinal disorders			
Hypoaesthesia oral			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	32		
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Paraesthesia oral			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 40		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Skin burning sensation subjects affected / exposed occurrences (all)	 0 / 52 (0.00%) 0 5 / 52 (9.62%) 38		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 0 / 52 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2017	Protocol v3.0 (06 October 2017)

Notes:

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.

There was a limitation for reporting some data within the EudraCT database in AEs and primary endpoint due to study being a two parts study and only second part with a cross-over design. Further information can be found in relevant section.

Notes: