EU Clinical Trials Register

Clinical trial results:
SAICoDis – Safety of Argatroban Infusion in Conduction Disturbances. A prospective, open, multicenter safety study to investigate conduction disturbances in patients receiving argatroban therapy.

Summary

EudraCT number	2016-003521-42
Trial protocol	DE
Global end of trial date	06 May 2021

Results information

Result version number	v2 (current)
This version publication date	09 September 2023
First version publication date	21 October 2022
Version creation reason	• Correction of full data set Correction of a primary end point value - standard deviation at Centre 2.

Trial information

Trial identification

Sponsor protocol code	ARG-E08

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mitsubishi Tanabe Pharma GmbH
Sponsor organisation address	Willstätterstr. 30, Düsseldorf, Germany, 40549
Public contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com
Scientific contact	Scientific Medical Adviser, Mitsubishi Tanabe Pharma GmbH, o.grapenthin@mt-pharma-de.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	12 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2021
Global end of trial reached?	Yes
Global end of trial date	06 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the change of QTc interval during argatroban infusion in patients undergoing PCI. To observe whether argatroban had a pharmacological effect on cardiac repolarization it was investigated, if a mean QTc prolongation of more than 10 ms occured between ECG-2, which needed to be performed immediately after cardiac intervention in a status of full anticoagulation with argatroban and ECG-1, the baseline ECG.

Protection of trial subjects:

The study was conducted in accordance with the 2013 (Fortaleza) revision of the 1964 Declaration of Helsinki, Good Clinical Practice as required by the International Conference on Harmonisation guidelines, applicable regional and local legislation, and standard operating procedures in place at Mitsubishi Tanabe Pharma GmbH, Mitsubishi Tanabe Pharma Europe Ltd. and at the contracted vendor.

All participants underwent screening aimed at minimising the likelihood and impact of potential risks of argatroban. In addition, regular safety monitoring during the study period for all participants ensured that any unanticipated effects of study participation were identified promptly and managed appropriately. Risk minimisation measures were also employed during the study as per the risk-benefit assessment for potential anticipated risks.

A subject was to be withdrawn if any of the following criteria were met:
- Patients have the right to withdraw from the study at any time for any reason.
- The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs and treatment failure, administrative reasons or other reasons.
-Women of childbearing potential or less than one year after menopause (unless surgically sterile) needed to show a negative pregnancy test at screening.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	18 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	24
From 65 to 84 years	25
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Eligible patients were recruited from a patient population who was diagnosed with stable coronary artery disease or unstable angina (troponin negative) undergoing elective PCI or patients in which only angiography was planned. The physician identified suitable patients by pre-screening medical records at the study centre.

Pre-assignment

Screening details:

Screening assessments were performed from hour -72 to -12. These assessments included written informed consent, demography, height, bodyweight, medical history, past and concomitant treatment, vital signs, verification of inclusion/ exclusion criteria, blood analysis, urine texts, 12-lead ECG. A total of 60 subjects were screened.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Treatment in this clinical trial is open.

However, to minimize bias, a central ECG reader (cardiac specialist) was blinded to patient data (patient ID, name, initials and birth date) and the time point on which the ECG was taken. In addition, automatically evaluated and printed ECG data (e.g. QT interval and diagnostic data) was blackened. Finally, each blinded ECG recording was pseudonymised manually by adding a unique number.

Arms

Arm title	Overall trial

Arm description:

Patients received an intravenous (i.v.) bolus of 300 µg/kg argatroban administered over a span of 3 to 5 minutes followed by the i.v. infusion of argatroban at 20 µg/kg/min until the end of the procedure. ACT was checked 5 minutes after bolus dose.
If ACT remained below the target of 300 s, the patient received an additional i.v. bolus injection of 150 µg/kg and the infusion dose was raised up to 30 µg/kg/min.
In cases ACT > 450 s, the infusion was reduced to 15 µg/kg/min and the value was checked again after 5 minutes.
As soon as the target ACT (between 300 s and 450 s) was reached, infusion dose remained unchanged during the PCI procedure.
Depending on clinical relevancy further ACT assessments were possible.

Arm type	Experimental
Investigational medicinal product name	Argatra® Multidose
Investigational medicinal product code	ARG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Patients received an intravenous (i.v.) bolus of 300 µg/kg argatroban administered over a span of 3 to 5 minutes followed by the i.v. infusion of argatroban at 20 µg/kg/min until the end of the procedure. ACT was checked 5 minutes after bolus dose. If ACT remained below the target of 300 s, the patient received an additional i.v. bolus injection of 150 µg/kg and the infusion dose was raised up to 30 µg/kg/min. In cases ACT > 450 s, the infusion was reduced to 15 µg/kg/min and the value was checked again after 5 minutes. As soon as the target ACT (between 300 s and 450 s) was reached, infusion dose remained unchanged during the PCI procedure. Depending on clinical relevancy further ACT assessments were possible.

Number of subjects in period 1	Overall trial
Started	50
Completed	49
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
All the patients of the enrollment set in whom argatroban was administered (ITT population).	

Reporting group values	Overall trial	Total	
Number of subjects	50	50	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	25	25	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	64.50		
standard deviation	± 10.43	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	39	39	
Stable CAD and/or unstable angina (troponin negative)			
Angina pectoris			
Units: Subjects			
Stable	40	40	
Unstable	9	9	
N/A	1	1	
ECG at screening without changes that impair assessment of QTc interval			
Units: Subjects			
Yes	50	50	
No	0	0	
Ethnicity			
Units: Subjects			
White	49	49	
Black	1	1	
Height, weight, BMI			
BMI (kg/m²; n=50)			
Units: Subjects			
Normal weight (18.5 - < 25 kg/m²)	12	12	

Pre-obesity (25 - < 30 kg/m²)	20	20	
Obesity class I (30 - < 35 kg/m²)	11	11	
Obesity class II (35 - < 40 kg/m²)	5	5	
Obesity class III (>= 40 kg/m²)	2	2	

Pregnancy test

Patient at least one year after menopause or surgically sterile (n=11).

Units: Subjects			
Yes	11	11	
N/A	39	39	

Classification for patients with stable Angina pectoris

n=40 patients

Units: Subjects			
CCS I	6	6	
CCS II	14	14	
CCS III	20	20	
N/A	10	10	

Maximal stenosis severity pre-PCI

Units: percent			
arithmetic mean	72.72		
standard deviation	± 27.65	-	

Height

Units: centimetre			
arithmetic mean	175.02		
standard deviation	± 9.69	-	

Weight

Units: kilogram(s)			
arithmetic mean	89.86		
standard deviation	± 20.22	-	

BMI

Units: kilogram(s)/square metre			
arithmetic mean	29.22		
standard deviation	± 5.78	-	

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All the patients of the enrolment set in whom argatroban was administered.

Subject analysis set title	ITT population/Subgroup Male
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Gender Male (subjects from ITT population).

Subject analysis set title	ITT population/Subgroup Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Gender Female (subjects from ITT population).

Subject analysis set title	ITT population/Centre 01
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Centre 01 (subjects from ITT population).

Subject analysis set title	ITT population/Centre 02
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Centre 02 (subjects from ITT population).

Reporting group values	ITT population	ITT population/Subgroup Male	ITT population/Subgroup Female
Number of subjects	50	39	11
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)	24	21	3
From 65-84 years	25	18	7
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	64.50	63.23	69
standard deviation	± 10.43	± 10.51	± 9.2
Gender categorical			
Units: Subjects			
Female	11	0	11
Male	39	39	0
Stable CAD and/or unstable angina (troponin negative)			
Angina pectoris			
Units: Subjects			
Stable	40	33	7
Unstable	9	6	3
N/A	1	0	1
ECG at screening without changes that impair assessment of QTc interval			
Units: Subjects			
Yes	50	39	11
No	0	0	0
Ethnicity			
Units: Subjects			
White	49	38	11
Black	1	1	0
Height, weight, BMI			
BMI (kg/m²; n=50)			
Units: Subjects			
Normal weight (18.5 - < 25 kg/m²)	12	6	6
Pre-obesity (25 - < 30 kg/m²)	20	17	3
Obesity class I (30 - < 35 kg/m²)	11	11	0
Obesity class II (35 - < 40 kg/m²)	5	5	0

Obesity class III (>= 40 kg/m²)	2	0	2
Pregnancy test			
Patient at least one year after menopause or surgically sterile (n=11).			
Units: Subjects			
Yes	11	0	11
N/A	39	0	0
Classification for patients with stable Angina pectoris			
n=40 patients			
Units: Subjects			
CCS I			
CCS II			
CCS III			
N/A			
Maximal stenosis severity pre-PCI			
Units: percent			
arithmetic mean			
standard deviation	±	±	±
Height			
Units: centimetre			
arithmetic mean	175.02	178	164.45
standard deviation	± 9.69	± 8.13	± 7.13
Weight			
Units: kilogram(s)			
arithmetic mean	89.86	93.49	77.0
standard deviation	± 20.22	± 17.45	± 24.75
BMI			
Units: kilogram(s)/square metre			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	ITT population/Centre 01	ITT population/Centre 02	
Number of subjects	25	25	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	14	
From 65-84 years	14	11	
85 years and over	1	0	
Age continuous			
Units: years			
arithmetic mean	66.28	62.72	
standard deviation	± 10.60	± 10.16	

Gender categorical Units: Subjects			
Female	7	4	
Male	18	21	
Stable CAD and/or unstable angina (troponin negative)			
Angina pectoris Units: Subjects			
Stable	19	21	
Unstable	6	3	
N/A	0	1	
ECG at screening without changes that impair assessment of QTc interval Units: Subjects			
Yes	25	25	
No	0	0	
Ethnicity Units: Subjects			
White	24	25	
Black	1	0	
Height, weight, BMI			
BMI (kg/m²; n=50) Units: Subjects			
Normal weight (18.5 - < 25 kg/m²)	7	5	
Pre-obesity (25 - < 30 kg/m²)	10	10	
Obesity class I (30 - < 35 kg/m²)	4	7	
Obesity class II (35 - < 40 kg/m²)	2	3	
Obesity class III (>= 40 kg/m²)	2	0	
Pregnancy test			
Patient at least one year after menopause or surgically sterile (n=11).			
Units: Subjects			
Yes	7	4	
N/A	18	21	
Classification for patients with stable Angina pectoris			
n=40 patients			
Units: Subjects			
CCS I			
CCS II			
CCS III			
N/A			
Maximal stenosis severity pre-PCI Units: percent			
arithmetic mean			
standard deviation	±	±	
Height Units: centimetre			
arithmetic mean	172.44	177.6	
standard deviation	± 8.90	± 9.92	
Weight Units: kilogram(s)			
arithmetic mean	93.49	92.92	

standard deviation	± 17.31	± 22.70	
BMI Units: kilogram(s)/square metre arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Patients received an intravenous (i.v.) bolus of 300 µg/kg argatroban administered over a span of 3 to 5 minutes followed by the i.v. infusion of argatroban at 20 µg/kg/min until the end of the procedure. ACT was checked 5 minutes after bolus dose.
If ACT remained below the target of 300 s, the patient received an additional i.v. bolus injection of 150 µg/kg and the infusion dose was raised up to 30 µg/kg/min.
In cases ACT > 450 s, the infusion was reduced to 15 µg/kg/min and the value was checked again after 5 minutes.
As soon as the target ACT (between 300 s and 450 s) was reached, infusion dose remained unchanged during the PCI procedure.
Depending on clinical relevancy further ACT assessments were possible.

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All the patients of the enrolment set in whom argatroban was administered.

Subject analysis set title	ITT population/Subgroup Male
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Gender Male (subjects from ITT population).

Subject analysis set title	ITT population/Subgroup Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Gender Female (subjects from ITT population).

Subject analysis set title	ITT population/Centre 01
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Centre 01 (subjects from ITT population).

Subject analysis set title	ITT population/Centre 02
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Centre 02 (subjects from ITT population).

Primary: Mean difference in QTc interval between ECG-2 and ECG-1

End point title	Mean difference in QTc interval between ECG-2 and ECG-1[1]

End point description:

It was investigated if a mean QTc prolongation of more than 10 ms occurred between ECG-2 and ECG-1.

P-values were as follows:
ITT population: <0.0866
ITT population/Subgroup Male: <0.0195
ITT population/Subgroup Female: <0.8863
ITT population/Centre 01: <0.7085
ITT population/Centre 02: <0.0076

End point type	Primary

End point timeframe:

ECG-2 was recorded immediately after cardiac intervention when patient was fully anticoagulated with argatroban and ECG-1 was recorded at baseline prior to first bolus dose of argatroban (argatroban-free status).

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 system does not allow for statistical analysis for single arm studies. P-values are provided in the end point description.

End point values	ITT population	ITT population/Subgroup Male	ITT population/Subgroup Female	ITT population/Centre 01
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	39	11	25
Units: millisecond(s)				
arithmetic mean (standard deviation)				
Prolongation of QTc >10 ms	0.94 (± 46.37)	-5.8936 (± 46.4072)	25.1460 (± 39.0616)	15.0046 (± 44.9538)

End point values	ITT population/Centre 02			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: millisecond(s)				
arithmetic mean (standard deviation)				
Prolongation of QTc >10 ms	-13.1343 (± 44.2363)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2

End point title	Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2

End point description:

Number of patients of ITT population exhibiting QTc interval of > 500 ms.

End point type	Secondary

End point timeframe:

ECG-2 immediately after argatroban infusion.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: number of patients	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the beginning of the study (date of treatment visit) to the study termination (after completion of ECG-3 measurement).

Adverse event reporting additional description:

All AEs encountered during the clinical study will be reported on the AE page of the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Vascular disorders			
Vascular stent thrombosis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)		
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2017	Protocol change to v1.2: Change of patient recruitment.
09 January 2019	Protocol change to v1.6: Restart of interrupted study.
10 December 2020	Protocol change to v2.0: Change from mono-centre to multi-centre study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 June 2018	In 2 of 13 treated patients experienced SAEs, one of which was considered "not study drug related", the second one led to the interruption (cause of event: study treatment; related to study medication/SUSAR; outcome: resolving).	09 January 2019

Notes:

Limitations and caveats

None reported