Clinical Study Protocol

Protocol Number: ARG-E08

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

Version Number: 2.0
Date: 08 May 2020
NCT number: NCT05740371

Trial protocol

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

Sponsor

Mitsubishi Tanabe Pharma GmbH
Willstaetterstraße 30
40549 Düsseldorf

Principal Coordinating Investigator

[redacted]

Version 2.0 of 08-May-2020

Protocol number: ARG-E08

EudraCT number: 2016-003521-42

I. Protocol signatures page

I have thoroughly read and reviewed the above-mentioned study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the trial protocol, international good clinical practice principles, the applicable regulations and laws and regulatory authority requirements.

Principal Coordinating Investigator

[redacted]

[redacted]

I have thoroughly read and reviewed the above-mentioned study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the trial protocol, international good clinical practice principles, the applicable regulations and laws and regulatory authority requirements.

Sponsor, Medical contact

[redacted]

I have thoroughly read and reviewed the above-mentioned study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the trial protocol, international good clinical practice principles, the applicable regulations and laws and regulatory authority requirements.

CRO, Project management

[redacted]

[redacted]

CRO, Statistician

[redacted]

[redacted]

II. Center specific signature page

I have thoroughly read and reviewed the above-mentioned study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the trial protocol, international good clinical practice principles, the applicable regulations and laws and regulatory authority requirements.

Name	Function	Date	Signature
	Further Investigators, Study Nurse, Study-Coordinator		

III. Table of contents

IV. List of tables

V. List of figures

VI. Abbreviations

ACT	Activated clotting time
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine-aminotransferase
AMG	„Arzneimittelgesetz" (germ.), (eng. „Federal Drug Law")
ASA	Acetylsalicylic acid
AST	Aspartate-aminotransferase
aPTT	Activated partial thromboplastin time
BfArM	„Bundesinstitut für Arzneimittel und Medizinprodukte" (germ.), (eng. „federal institute for drugs and medical devices")
CAD	Coronary artery disease
CRF	Case report form
CRO	Contract research organisation
DAPT	Dual antiplatelet therapy
dl	Deciliter
DOAC	Direct oral anticoagulants
DSGVO	"Datenschutz-Grundverordnung"
dTT	Diluted Thrombin Time
ECG	Electrocardiogram
ECG-1	12-lead baseline electrocardiogram performed at screening visit
ECG-2	12-lead electrocardiogram performed immediately after cardiac intervention in steady

	state anticoagulation with argatroban.
ECG-3	12-lead electrocardiogram performed > 8 but ≤ 28 hours after termination of prolonged argatroban infusion.
e.g.	exempli gratia (lat.), (eng. "for example")
FPFV	First patient first visit (start of enrolment)
g	Gram
GCP	Good clinical practice
GCP-V	"Good clinical practice – Verordnung" (germ.)
GFR	Glomerular filtration rate
γGT	Gamma-glutamyl transpeptidase
HIT	Heparin-induced thrombocytopenia
ICH	International conference for harmonisation
ICMJE	International committee of medical journal editors
i.e.	Id est (lat.), (eng. "that is")
IEC	Independent ethics committee
ITT	Intention to treat population
IMP	Investigational medicinal product
INR	International normalised ratio
i.v.	Intravenous
kg	Kilogram
l	Liter
LPFV	Last patient first visit (end of enrolment)
LPLV	Last patient last visit (last patient out)
MedDRA	Medical dictionary for regulatory activities
mmHg	Millimeter of mercury
ms	Milliseconds
min	Minutes
PASS	Post authorization safety study
PCI	Percutaneous coronary intervention

PP	Per protocol
Q	Quarter (calendar)
QTc	Corrected QT interval
s	Seconds
SAE	Serious adverse event
SAP	Statistical analysis plan
SDV	Source data verification
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SmPC	Summary of product characteristics (Fachinformation)
µg	Microgram
UFH	Unfractionated heparin
ULN	Upper limit of the normal
VKA	Vitamin K antagonists

1. Organisational and administrative aspects of the trial

1.1. Central organisation units

SPONSOR

Mitsubishi Tanabe Pharma GmbH
Willstaetterstr. 30
40549 Düsseldorf

Sponsor scientific contact

[redacted]

AE Management

QPPV
Mitsubishi Tanabe Pharma Europe Ltd EU

[redacted]

PRINCIPAL COORDINATING INVESTIGATOR

[redacted]

CLINICAL RESEARCH ORGANIZATION (CRO)

[redacted]

Project management & Monitoring

[redacted]

Data Management and Statistics

[redacted]

1.2. Internal data monitoring regarding safety

Internal data monitoring will be performed by the deputy investigator of the study site [redacted] and by sponsor's [redacted]
They will all have immediate access to the ECG data and to all serious adverse events. In case ECG data shows substantial prolongation of QTc in a number of ≥ 30% patients or other events regarding safety are detected, the experts will advise the sponsor, the investigator and the project manager with regard to continuing the trial (e.g. termination or modification).

1.3. Study laboratories and other technical services

ECG evaluation will be performed by

at least two experienced cardiac specialists of
[redacted]

Laboratory argatroban plasma concentration via dTT will be analysed by
[redacted]

1.4. Investigators and trial sites

This clinical trial will be carried out as a multicenter, open label trial at 2 trial sites in Germany. If necessary, further qualified trial sites may be recruited to the trial.

The investigator must ensure that this protocol (and any amendments and/or supplements) is carried out in accordance with existing laws and regulations, the ICH-GCP guidelines, the Helsinki principles and the provisions of the AMG.

Every participating patient must have signed a written informed consent prior to study start.
The investigator must have read and understood this trial protocol and attached appendices and any amendments and/or supplements thereto.

1.5. Financing

The clinical trial will be financed by Mitsubishi Tanabe Pharma GmbH, Willstaetterstr. 30, 40549 Düsseldorf in Germany.

2. Synopsis

Sponsor	Mitsubishi Tanabe Pharma GmbH Willstaetterstraße 30 40549 Düsseldorf
Principal Coordinating Investigator	[redacted]
Title of the clinical trial	SAICoDis - Safety of Argatroban Infusion in Conduction Disturbances. A prospective, open, multicenter safety study to investigate conduction disturbances in patients receiving argatroban therapy.
Study phase	Phase IV, interventional safety study (PASS)
Type of trial, trial design, methodology	The present study is a prospective, multicenter, single-group, open-label, ECG-reader (cardiac specialist) blinded safety study to investigate conduction disturbances in patients receiving argatroban therapy during an elective percutaneous coronary intervention (PCI).
Number of study centers	2 centers
Sample size	50
Target population and Inclusion/Exclusion criteria	Eligible patients will be recruited from a patient population who has been diagnosed with stable coronary artery disease (CAD) or unstable angina (troponin negative) and who will be undergoing elective PCI at the study center. **Inclusion criteria**: • Diagnosis of stable CAD or unstable angina (troponin negative, i.e. within the normal range for the study site) with low to moderate anatomic risk. • Patient requires elective percutaneous coronary angioplasty or stent insertion with an approved device in one or more de novo-treated or re-stenotic lesions in native vessels.

- Patient is on adequate platelet inhibition therapy after receiving a loading dose with ASA and clopidogrel before start of intervention
- Willingness to give written informed consent, written consent for data protection (legal requirement in Germany "datenschutzrechtliche Einwilligung") and willingness to participate and to comply with the requirements of the study protocol.
- The patient (female/male) is at least 18 years of age.
- Baseline ECG without changes that impair assessment of QTc interval.

Exclusion criteria:

General exclusion criteria:

- Patient is indicated for highly complex 3-vessel intervention.
- The female patient is pregnant (exclusion by routine urine test) or is nursing during the therapy period.
- Patient who participates currently in another clinical trial or patients who participated in another clinical trial during the last 3 months prior to study start (date of treatment visit).
- History of drug, alcohol or chemical abuse within 6 months prior to study start.
- Planned surgical intervention other than study procedure within 7 days after study start.
- Any condition, which contraindicates the use of argatroban, or endangers the patient if he/she participated in this study.

Factors influencing QTc interval:

- Marked prolongation of QTc interval (defined as repeated demonstration of a QTc interval > 450 ms) at baseline ECG.
- A history of risk factors of Torsade de pointes (e.g. heart failure, hypokalemia, family history of Long QT Syndrome).
- Known intraventricular conduction disturbance.
- Bradycardia: heart rate < 45 min^{-1}.
- Electrolyte level outside normal range.
- The use of concomitant medications that interfere with the QTc interval.
- Intake of digitalis within the last 2 weeks before study start.

	• Acute myocardial infarction or troponin positive unstable angina. Factors inhibiting use of argatroban in this study: • Intolerance to ingredients of Argatra® (sorbitol). • Known cirrhosis, hepatitis, clinically significant hepatic disorder at study start and history of clinically relevant hepatic disorder. • Current hepatic disorder indicated by laboratory liver profile at screening: Bilirubin, AST/SGOT, ALT/SGPT, γGT > 3.0 times upper limit of the normal (ULN). • Renal insufficiency indicated by laboratory renal profile at screening: GFR < 35 ml/min. • Uncontrolled hypertension (defined as blood pressure >180/120 mmHg). • If any form of heparin was taken prior to study start **and** aPTT ≥ 35 s. • Taking direct oral anticoagulants (DOAC) within 1 month prior to study start. • If anticoagulants of type of vitamin K antagonists (VKA) were taken prior to study start **and** INR >1.2. • Platelet count <125 x 10^9/l. • Documented coagulation disorder or bleeding diathesis. • Uncontrolled haemorrhage within the past 3 months. • Uncontrolled peptic ulcer disease or gastrointestinal bleeding within the past 3 months. • Cerebral aneurysm. • Haemorrhagic stroke or ischaemic stroke in the past 6 months.
Primary trial objective	The primary objective is to determine change of QTc interval during intravenous argatroban infusion in patients undergoing PCI. To observe whether argatroban has a pharmacological effect on cardiac repolarization, it will be investigated, if a mean QTc prolongation of more than 10 ms will occur between ECG-2 (ECG immediately after cardiac intervention when patient is fully anticoagulated with argatroban) and ECG-1 (baseline ECG).

Study end points	Primary endpoint: The primary endpoint of this study is the mean difference in QTc interval between ECG-2 and ECG-1. Secondary endpoints: • Mean difference in QTc interval between ECG-3 (ECG > 8 but ≤ 28 hours after termination of prolonged argatroban infusion) and ECG-1. Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2. • Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-3. • Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-2 compared to ECG-1. • Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-3 compared to ECG-1. • Incidence of haemorrhagic events according to the definition of CABG-related bleeding. • Incidence of adverse events.
Safety variables	• QTc • ACT • Incidence of haemorrhagic events • Incidence of adverse events
Name of investigational medicinal product (IMP)	Argatroban-monohydrate
Dosage and method of administration (IMP)	Patients will receive 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 will be checked 5 minutes after bolus dose. If ACT remains below the target of 300 s, the patient receives an additional i.v. bolus injection of 150 µg/kg and the infusion dose will be raised up to 30 µg/kg/min. In cases ACT > 450 s, the infusion will be reduced to 15 µg/kg/min and the value will be checked again after 5 minutes. As soon as the target ACT (between 300 s and 450 s) is reached, infusion dose shall remain unchanged during the PCI procedure.

	Depending on clinical relevancy further ACT assessments are possible.
Therapy used as a comparator	none
Duration of treatment	Study duration for each patient depends on the clinical routine of PCI treatment at site since argatroban therapy is part of this coronary intervention. The administration of the study drug argatroban is restricted to the duration of the PCI procedure. That means the argatroban infusion will be stopped with end of intervention (removal of the guiding catheter or the sheath). The study ends for the patient with completion the ECG-3 measurement > 8 but ≤ 28 hours after PCI.
Duration of study	First patient first visit (FPFV): Q1 2017 Last patient first visit (LPFV): Q1 2021 End of study (LPLV): Q1 2021 Final study report: Q4 2021
Statistician	[redacted]
Statistical methods	The following measurements of QTc will be made for each patient: • Prior to first bolus dose of argatroban = QTc_1 • Immediately after cardiac intervention in a status of full anticoagulation with argatroban = QTc_2 • > 8 but ≤ 28 hours after termination of prolonged argatroban infusion = QTc_3 The statistical hypothesis of this study refers to the difference QTc_2 minus QTc_1 = Δ QTc: H_0: Δ QTc > 10 ms H_A: Δ QTc ≤ 10 ms

	H_0 will be tested by a one-sided one sample t-test with a significance level of alpha = 5%. Data from all patients with measurements QTc_1 and QTc_2 will be included in the analysis of Δ QTc. Additionally, Δ QTc as well as QTc_1 and QTc_2 will be described by descriptive statistics (mean, standard deviation, median, minimum, maximum, and 95%-confidence interval). An individual subject listing will be provided with QTc_1, QTc_2, Δ QTc, QTc_3 and the difference QTc_3 minus QTc_1. The analysis of the primary variable will be based on the ITT sample. It will be repeated for the PP sample. The study report will contain a statement about difference in study results between the ITT and PP sample. • Mean difference in QTc interval between measurements at ECG-3 and ECG-1. The difference QTc_3 minus QTc_1 will be described by descriptive statistics. If the 95%-confidence interval will include the value 0, it will be said that QTc-values returned to their baseline values. • Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2. • Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-3. • Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-2 compared to ECG-1. • Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-3 compared to ECG-1. One-sided 95%-Pearson-Clopper confidence limits will be computed for those proportions. • Incidence of haemorrhagic events according to the definition of CABG-related bleeding. A two-sided 95%-Pearson-Clopper confidence limit will be computed for the proportion of patients with haemorrhagic events.
GCP conformance	The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revision (October 2013, 64th General Assembly of the World Medical Association, Fortaleza, Brazil).

	The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation (especially the Federal Drug Law [AMG] and the GCP-V).
Financing	The clinical trial will be financed by Mitsubishi Tanabe Pharma GmbH Willstaetterstr. 30 40549 Düsseldorf

3. Flow chart

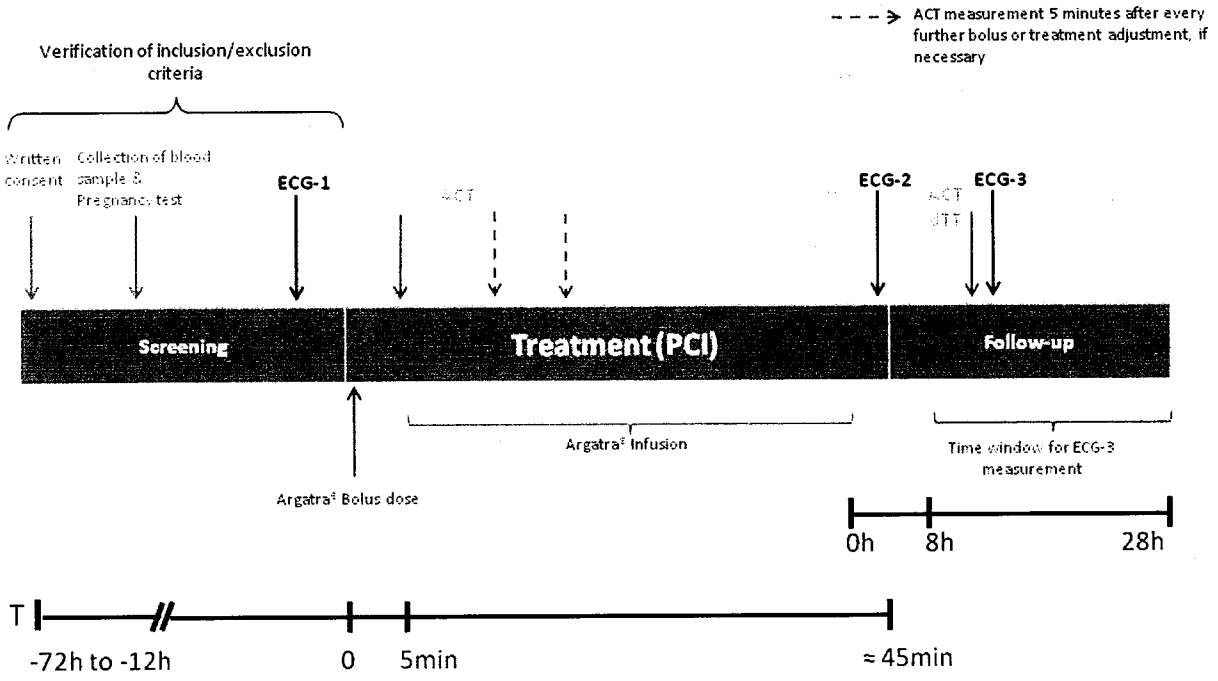

Figure 1: Timing of study procedures

3.1. Schedule of assessment

Day/ visit type ► procedures ▼	**Screening** (hour -72 to -12)	**Treatment** (hour 0)	**Follow-Up** (ends > 8 but ≤ 28 hours after PCI)
Informed consent	✓		
Inclusion/exclusion	✓		
Demographics	✓		
Medical history	✓		
Past & concomitant treatment	✓	✓	✓
Vital signs and bodyweight	✓		
Pregnancy test (urine)	✓		
ECG	✓	✓	✓
Hematology	✓		
Hematocrit	✓	(✓)	✓
Hs-Troponin-T	✓		
Liver function profile	✓		
Coagulation profile	✓	✓	✓
Kidney function profile	✓		
Electrolytes	✓		
Study drug infusion		✓	
AE evaluation		✓	✓

4. Introduction

The introduction of coronary stents broadened the indications for cardiac catheterization and PCIs [1]. Unfractionated heparin (UFH) is one standard therapy to achieve complete and sustained coronary artery recanalization. The major limitation of heparin is the emergence of heparin-induced thrombocytopenia (HIT), a life- and limb-threatening immune hematological reaction associated with thrombocytopenia. With the innovation of coronary stents in the management of patients with CAD, cardiac patients are more frequently exposed to heparin and therefore are at an increased risk to develop a potential complication such as HIT [2].

Argatroban has been approved for suitable alternative anticoagulation in patients with or at risk of HIT. Extension of the approval for the use of argatroban in non-HIT II patients was not aspired by the sponsor yet.

The synthetic arginine-derived direct thrombin inhibitor argatroban is an attractive anticoagulant for (PCI), because of its rapid onset and offset, and its hepatic elimination. In addition to a short half-life, the reversible inhibition of thrombin leads to a well-defined control of its anticoagulation effect.

Argatroban has been shown to be a safe and effective anticoagulant during PCI in clinical studies. In three prospective studies (ARG-216, ARG-310, ARG-311) a total of 91 aspirin-treated patients with present or previous diagnosis of HIT were studied [3]. 112 procedures with a dose of 350 µg/kg given as an i.v. bolus plus 25 µg/kg/min as an i.v. infusion which was adjusted to activated clotting time (ACT) of 300 - 450 s were successfully achieved. In an open-label, non-randomized study the concomitant use of argatroban with aspirin and a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor was investigated [4]. Argatroban was dosed at 250 to 300 µg/kg bolus followed by a 15 µg/kg/min infusion and either abciximab or eptifibatide was administered simultaneously. Argatroban provided adequate anticoagulation with an acceptable bleeding risk.

Furthermore the ARG-E04 study could demonstrate in a prospective randomized controlled design, that argatroban dose-dependently and more effectively achieves ACT prolongation than UFH in patients undergoing elective stent-PCI with concomitant dual antiplatelet treatment of aspirin and clopidogrel [5].

HIT patients undergoing PCI are at particular risk of thrombosis and require greater anticoagulation levels. The data of previous studies [2,3] and the ARG-E04 study show that the reversible thrombin inhibition by argatroban translates into a well predictable on- and offset of anticoagulation without any major bleeding and no increased incidence of ischemic events [5].

In HIT-patients who require PCI or stenting procedures, replacing heparin with a direct thrombin inhibitor as anticoagulant has been suggested as a safe alternative option.

5. Objectives of the clinical trial

5.1. Rationale for the clinical trial

It is well known that some drugs being developed for uses other than control of arrhythmias can significantly prolong the QT/QTc interval as a part of their mechanism of clinical efficacy. The QT interval represents the duration of the beginning of depolarization until the end of depolarization in ventricular cardiomyocytes. A significantly increased QT interval could lead to development of the life- threatening polymorphic ventricular tachyarrhythmia "Torsade-de-pointes". The potential to prolong QTc interval is an adverse side effect known for approximately 2 – 3% of all drugs [6]. Parts of them were not subscribed due to arrhythmic heart disease but to infections or mental illnesses (like antidepressants and neuroleptics). Thus, the evaluation of drug effect on QT interval is highly recommended to reduce the risk of drug-induced arrhythmia that may lead to sudden death.

For planned market authorization in [redacted], safety data concerning conduction disturbances, particularly data about the QTc interval, have to be collected due to an obligation of [redacted]. Until now, no data on a possible QTc interval prolongation of argatroban has been gained.

Patients undergoing elective PCI are suitable candidates to determine QTc interval by electrocardiogram (ECG) during intervention. This patient subpopulation was chosen for this study as it does not suffer from emergency conditions requiring extensive care treatment. They are able to give consent to study procedures without impairment of mental state or consciousness. Additionally, these patients represent a group with a manageable amount of co-medication and thereby influence on QTc can be limited. ECG and blood samples have to be taken in any case during PCI; therefore, additional burden due to study procedures is low in these patients.

Based on its rapid onset and offset and its hepatic elimination, the synthetic arginine-derived direct thrombin inhibitor argatroban is a perfect anticoagulant for PCI patients. A previous pilot study showed that argatroban dose-dependently increased coagulation parameters and demonstrated a predictable anticoagulant effect in non-HIT patients undergoing PCI [5].

5.2. Primary objective

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

5.3. Secondary objectives

- Determination of the QTc interval after sufficient wash-out period by ECG-3 which needs to be performed > 8 but ≤ 28 hours after termination of prolonged argatroban infusion.
- Investigation of dependence of QTc interval on gender and applied doses.
- Determination of coagulation status during argatroban therapy.
- Assessment of safety-related events within the scope of anticoagulation with argatroban, for example bleeding events or thomboembolic events.

5.4. Primary endpoint

The primary endpoint of this study is the mean difference in QTc interval between ECG-2 and ECG-1.

5.5. Secondary endpoints

- Mean difference in QTc interval between ECG-3 and ECG-1.
- Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2.
- Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-3.
- Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-2 compared to ECG-1.
- Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-3 compared to ECG-1.
- Incidence of haemorrhagic events according to the definition of CABG-related bleeding.
- Incidence of adverse events.

6. Trial conduct

6.1. General aspects of trial design

The present study is an interventional Phase IV, prospective, multicenter, single-group, open-label, ECG-reader (cardiac specialist) blinded safety study (PASS) to investigate conduction disturbances in patients receiving argatroban therapy during an elective percutaneous coronary intervention (PCI).

6.2. Time plan

Study duration for each patient depends on the clinical routine of PCI treatment at site since argatroban therapy is part of this coronary intervention. The administration of the study drug is restricted to the duration of the PCI procedure (up to 1 hour). The study ends for the patient with completion of the last ECG measurement (ECG-3) > 8 but ≤ 28 hours after PCI.

Prior to study start, patients need to provide informed consent after having been given enough time for consideration. Time span between informing the patient and giving consent should be at least one night.

The study starts on the date of treatment (PCI) according to clinical routine. In order to verify all inclusion and exclusion criteria, a screening phase is preceded including clinical and laboratory assessments and a pregnancy test. Blood pressure and pulse rate will be measured, and finally a baseline 12-lead ECG (ECG-1) will be performed.

The PCI procedure is conducted according to clinical standard procedures and the protocol. Plasma samples will be obtained to assess ACT after the initial bolus of argatroban was given. All other medication should be executed as in daily routine.

Immediately after cardiac intervention, patients receive a second 12-lead ECG (ECG-2) in the catheter lab. At this point in time, the patient is still fully anticoagulated with argatroban (steady state status). The study ends when the last ECG > 8 but ≤ 28 hours after termination of argatroban infusion (ECG-3) has been conducted at follow-up of the PCI procedure (see figure 1).

All recordings of the three ECG measurements will be sent to a blinded ECG reader (cardiac specialist) who will provide assessment within 48 hours.

Following timing has been planned for the study:

First patient first visit (FPFV):	Q1 2017
Last patient first visit (LPFV):	Q1 2021
End of study (LPLV):	Q1 2021
Final study report:	Q4 2021

6.3. Treatment plan and methods

The physician selects suitable patients, i.e. patients with stable coronary artery disease or unstable angina (troponin negative) undergoing elective PCI, who meet all the required criteria within the scope of the study. The physician will identify suitable patients by pre-screening medical records. Only suitable patients are eligible for the following informed consent process and screening examinations.

The patient information sheet will be handed over to suitable patients in advance of the screening visit in order to allow patients time to read all the information, reflect and ask questions. By no later than screening visit, patients will be given a verbal description of the study and the procedures involved. Please refer to section 14.4 for detailed information regarding the informed consent process.
All patients who signed the informed consent and thereafter undergo screening activities must be listed in the Patient Screening Log.

Screening phase (hour -72 to -12):

After having obtain written informed consent from the patient at screening, the following clinical assessments will be performed prior to start of PCI: Demographics (age, gender and ethnicity), height, bodyweight, medical history (e.g. disorders of interest are cardiac, kidney and liver disease), past and concomitant treatment (drug treatment in the last 6 months and non-drug treatment) and vital signs (resting pulse rate, systolic and diastolic blood pressure measured in a sitting position). All patients will be assessed for eligibility within the inclusion and exclusion criteria.
Furthermore, laboratory blood samples of all patients will be collected. Women of childbearing potential or less than one year after menopause (unless surgically sterile) must show a negative pregnancy test at screening. For this purpose, urine samples of female patients will be used for a routine pregnancy test.
Blood samples will be immediately used for on-site determination of coagulation status by measuring INR (international normalized ratio) and aPTT (activated partial thromboplastin time). If the patient received any form of heparin prior to study enrollment, aPTT must not be equal or greater than 35 s. In case anticoagulant medication of type of vitamin K antagonists (VKA) was taken prior to study enrollment, INR must not exceed 1.2. DOAC are not allowed to be taken within 1 month prior to study enrollment. In addition to this, blood samples will also be used for analysis of a hemogram

(containing leucocytes, thrombocytes, hemoglobin, hematocrit), of liver function profile (bilirubin, AST/ SGOT, ALT/ SGPT, γGT), kidney function profile (serum creatinine, GFR), hs-troponin-T and electrolytes (Na, K, Ca). The collection and analysis of blood samples are in line with the clinical routine at site.
Blood analysis and urine tests will be analysed by the local laboratory at site.

Having ascertained all parameters are within the required range, a routine 12-lead ECG will be performed (ECG-1). The investigator needs to assess non-existence of conditions that prohibit readability of ECG and evaluation of QTc. A marked baseline prolongation of QTc interval (defined as repeated demonstration of a QTc interval > 450 ms) is an exclusion criterion.

Treatment phase (hour 0):

If a patient does not fulfill all criteria, this patient may not take part in the treatment phase and the PCI will be performed according to normal clinical routine by using standard anticoagulation treatment. If all inclusion criteria are fulfilled and all exclusion criteria can be excluded, this patient is able to participate in the treatment phase.

Inclusion of a new study patient will be reported by faxing a completed "Patient Registration Fax" sheet to the CRO[redacted]

All patients must receive a DAPT with a loading dose of clopidogrel and ASA as standard antithrombotic treatment for preparation of elective angiography with high probability for PCI, followed by appropriate maintenance DAPT treatment in line with the current guidelines [7] after intervention.

In general, 3 to 24 hours prior to intervention a clopidogrel loading dose of 600 mg will be administered. In addition to clopidogrel the patient receives a loading with 250 mg ASA (orally or i.v.). The early dual platelet inhibition therapy is applied due the rapid offset of the anticoagulation effect upon termination of argatroban infusion at the end of the PCI. The offset of argatroban effect has been observed within 30 minutes after stop of the infusion. Thus, a potential gap of sufficient antithrombotic protection may be obtained if the dual antiplatelet therapy is only started after termination of argatroban infusion. The ARG-E04 study [5] revealed an effective and safe persistent antithrombotic protection if dual antiplatelet therapy was instituted before PCI commenced.

After getting an argatroban bolus dose of 300 µg/kg (administered over 3 to 5 min), the patient receives an argatroban maintenance dose infusion of 20 µg/kg/min. The argatroban infusion will be stopped at the end of the PCI (removal of the guiding catheter or the sheath).

To monitor reliability of anticoagulation, ACT will be measured as a routine parameter of anticoagulation for PCI. In general, ACT measurements will be started and performed with the placement of the vascular sheath (starting the intervention). Therefore, plasma samples will be obtained 5 minutes after completion of injection of the bolus dose and at 5 min after completion of every further bolus or treatment adjustment. Depending on clinical relevancy further ACT assessments are possible.

If target ACT is reached, the intervention can be continued.

If ACT remains below the target of 300 s, patients will receive an additional i.v. bolus injection of 150 µg/kg and the infusion dose will be raised up to 30 µg/kg/min. In case ACT > 450 s, the infusion dose will be reduced to 15 µg/kg/min. As soon as the target ACT (between 300 s and 450 s) is reached infusion dose shall remain unchanged during PCI procedure. If clinically necessary, the hematocrit value will be measured during the treatment.

The PCI will be conducted according to usual clinical routine of the investigator site. The PCI starts with the placement of the vascular sheath and ends with re-movement of this sheath. Immediately after PCI, a study-specific 12-lead ECG (ECG-2) will be recorded in the catheter lab at a time of steady state anticoagulation with argatroban.

Follow-up phase (ends > 8 but ≤ 28h after PCI):

After PCI, the patient will be followed-up according to routine practice. As part of it, a third and last 12-lead ECG (ECG-3) will be performed > 8 but ≤ 28 hours after termination of argatroban infusion, at the end of argatroban wash-out period. Shortly before this ECG examination a blood sample of 5 ml should be taken to analyse the current haematocrit, final ACT value and the coagulation status (dTT) for assessing the argatroban plasma concentration. The final ACT measurement is intended to verify a pharmacodynamic effect of argatroban. The argatroban plasma concentration will be analysed in a batch procedure by central laboratory located at the [redacted]. For the measurement of dTT data the Hemoclot Thrombin Inhibitor assay calibrated with argatroban will be used.

An ACT value ≤ 160 s (ACT norm range: 80 - 160 s) indicates that no pharmacodynamic effect of argatroban is present in the blood circuit of the patient anymore. As soon as the argatroban-free status is indicated the ECG-3 record should be conducted. But in case ACT > 160 s the ECG-3 should be postponed until the intended ACT target of ≤ 160 s is reached. In any case, the time point of ECG-3 measurement should not exceed 28 hours after end of argatroban infusion. The study ends with completion of the ECG-3 measurement at this follow-up visit.

All ECG recordings of one patient will be numbered according to a list with random numbers for each patient ID and time point, and sent to a blinded central reader (blinded cardiac specialist).

6.4. Deviation from the study plan

The investigator must not deviate from the procedures described in the study protocol except if the safety of patients would be endangered.

Every protocol violation needs to be thoroughly documented and will be assessed as minor or major by the investigator and sponsor.

7. Trial population

7.1. Selection of trial population and assignment to treatment

The 50 patients to be included into the study will be recruited from patients who have been diagnosed with stable CAD or unstable angina (troponin negative) and who will be undergoing elective PCI at the study center.

Eligible patients who already signed the patient informed consent will be assigned a unique patient number (patient ID) at screening visit. The assigned patient ID of each patient has to be documented using a Patient Identification Log. The patient ID consists of two parts. The first part represents the center number, which is assigned to the investigator by the sponsor. The second part is the patient number which will be assigned sequentially within the center by the investigator. Once assigned to the patient, the patient number may not be reused.

7.2. Inclusion criteria

To be eligible for this trial, patients must meet following requirements:

- Diagnosis of stable CAD or unstable angina (troponin negative, i.e. within the normal range for the study site) with low to moderate anatomic risk.
- Patient requires elective percutaneous coronary angioplasty or stent insertion with an approved device in one or more de novo-treated or re-stenotic lesions in native vessels.
- Patient is on adequate platelet inhibition therapy after receiving a loading dose with ASA and clopidogrel before start of intervention
- Willingness to give written informed consent, written consent for data protection (legal requirement in Germany "datenschutzrechtliche Einwilligung") and willingness to participate and to comply with the requirements of the study protocol.
- The patient (female/male) is at least 18 years of age.
- Baseline ECG without changes that impair assessment of QTc interval.

7.3. Exclusion criteria

Patients with any of the following exclusion criteria will not be eligible for participation:

General exclusion criteria:

- Patient is indicated for highly complex 3-vessel intervention.
- The female patient is pregnant (exclusion by routine urine test) or is nursing during therapy period.
- Patients who are currently participating in another clinical trial or patients who participated in another clinical trial during the last 3 months prior to study start (date of treatment visit).
- History of drug, alcohol or chemical abuse within 6 months prior to study start.
- Planned surgical intervention other than study procedure within 7 days after study start.
- Any condition, which contraindicates the use of argatroban, or endangers the patient if he/she participated in this study.

Factors influencing QTc interval:

- Marked baseline prolongation of QTc interval (repeated demonstration of a QTc interval > 450 ms at baseline ECG).
- A history of risk factors of Torsade de pointes (e.g. heart failure, hypokalemia, family history of Long QT Syndrome).
- Known intraventricular conduction disturbance.
- Bradycardia: heart rate < 45 min^{-1}.
- Electrolyte level outside normal range (according to laboratory's reference values).
- The use of concomitant medications that interfere with the QTc interval.

- Intake of digitalis within the last 2 weeks before study start.
- Acute myocardial infarction or troponin-positive unstable angina.

Factors inhibiting use of argatroban in this study:

- Intolerance to ingredients of Argatra® (sorbitol).
- Known cirrhosis, hepatitis, clinically significant hepatic disorder at study start and/or history of clinically relevant hepatic disorder.
- Current hepatic disorder indicated by laboratory liver profile at screening: Bilirubin, AST/SGOT, ALT/SGPT, γGT > 3.0 times upper limit of the normal (ULN).
- Renal insufficiency indicated by laboratory renal profile at study start: GFR < 35 ml/min.
- Uncontrolled hypertension (defined as blood pressure >180/120 mmHg).
- If any form of heparin was taken prior to study start **and** aPTT ≥ 35 s.
- Intake of direct oral anticoagulants (DOAC) within 1 month prior to study start.
- If anticoagulants of type of vitamin K antagonists (VKA) were taken prior to study start **and** INR >1.2.
- Platelet count <125 x 10^9/l.
- Documented coagulation disorder or bleeding diathesis.
- Uncontrolled haemorrhage within the past 3 months.
- Uncontrolled peptic ulcer disease or gastrointestinal bleeding within the past 3 months.
- Cerebral aneurysm.
- Haemorrhagic stroke or ischaemic stroke in the past 6 months.

8. Treatment

8.1. Study medication

According to § 3 (3) GCP-V an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. In this study argatroban (trade name Argatra® Multidose) is the investigational medicinal product and neither placebo nor any comparator is used.

Investigational Medicinal Product

Argatra® is supplied in individually packaged vials as a concentrate for solution for infusion.

Active agent: [redacted]

Pharmaceutical classification: [redacted].

Chemical name: [redacted]

[redacted]

Molecular weight: [redacted]

Molecular formula: [redacted]

Application: [redacted]

Qualitative and quantitative composition of the concentrate:

Ingredient	Concentration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.2. Dose and schedule of treatment

Efficacy and safety of argatroban have been investigated in the treatment of PCI patients without HIT II previously [5].

Patients will receive argatroban treatment in a dosing schedule adapted from the approved Argatra® Multidose SmPC with information status by July 2016, taking into account that due to the lack of HIT II in the study population a lower bolus and maintenance dose led to a rapid and sufficient anticoagulatory effect in the previous ARG-E04 study [5].

Since the anticoagulation effect of argatroban returns rapidly towards normal level, a possible gap in a sufficient continuous antithrombotic protection must be closed. To reduce the risk of early stent thrombosis, patients receive in accordance with the ARG-E04 study a dual platelet inhibition therapy with the **antiplatelet drugs** clopidogrel and ASA before start of the PCI. A clopidogrel loading dose of 600 mg is administered 3 to 24 hours prior to an elective angiography with high probability for PCI. In addition to clopidogrel, all patients receive a loading of 250 mg ASA (orally or i.v.). For patients on chronic DAPT with ASA and clopidogrel known being loaded there is no need for an additional loading prior to intervention.
After PCI, antithrombotic prophylaxis with DAPT will be conducted according to clinical routine and ESC guidelines.

With regard to treatment with the **anticoagulant** study medication argatroban, the patient will receive an i.v. bolus of 300 µg/kg argatroban administered over a span of 3 to 5 minutes before start of the intervention procedure, followed by the i.v. infusion of argatroban at 20 µg/kg/min until the end of the procedure. ACT will be checked 5 minutes after the initial bolus dose was administered. If ACT remains below the target of 300 s, the patient receives an additional i.v. bolus injection of 150 µg/kg and the infusion dose will be raised up to 30 µg/kg/min. In cases ACT > 450 s, the infusion will be reduced to 15 µg/kg/min and the value will be checked again after 5 minutes. As soon as the target ACT (between 300 s and 450 s) is reached, infusion dose shall remain unchanged during the PCI procedure. Depending on clinical relevancy further ACT assessments are possible.

8.3. Manufacture and labeling of IMP

The sponsor supplies the investigational site with an approved and authorized medicinal product as commodities. Thus a labeling in accordance with § 5 of the GCP-Verordnung (GCP-V) [8] is not intended.

8.4. Storage, dispensing and return of IMP

The vial is kept in the packaging to protect from light and stored at room temperature.

The investigator must maintain accurate records accounting for the receipt and disposition of the IMP. Therefore, a preprinted drug dispensing log is provided to the site. This log must identify the patient and must be kept current. Furthermore, the amount of medication administered to each patient at each visit (with corresponding dates) must be documented on it. All medication supplies (empty containers, as well as partly used and unused medication) must be made available for inspection at every monitoring visit. Depending on local regulations all unused medication, partly used and empty packages can either be returned to the sponsor or destroyed at site. In any case the return or destruction must be documented accordingly.

8.5. Assignment of patients to treatment groups

This clinical trial is a single-group study.

8.6. Blinding and unblinding

Treatment in this clinical trial is open.

However, to minimize bias, a central ECG reader (cardiac specialist) will be blinded to the investigational site, patient data (patient ID, name, initials and birth date) and the time point on which the ECG was taken. In this way the blinded reader is not able to identify if the ECG was taken before (ECG-1), during (ECG-2) or after (ECG-3) the treatment with argatroban. In addition, automatically evaluated and printed ECG data (e.g. QT interval and diagnostic data) will be blackened in order to reduce any influence on the evaluation result provided by the blinded cardiac specialist.
Finally, each blinded ECG recording will be pseudonymized manually by adding a unique number. Therefore, a table with pseudonymization numbers will be provided to the site. The unique number identifies the investigational site, patient and the time of ECG measurement.

The process of blinded ECG assessment is defined as follows: The investigational site adds the respective pseudonymization number on the ECG record and sends the record to responsible personnel of the blinding team of the cardiology department of the [redacted], who rechecks the pseudonymization number and finally blackens the ECG record. The responsible personnel forwards the blackened and pseudonymized ECG record to a blinded cardiac specialist. The blinded cardiac specialist will provide her/his assessment in a timely manner by means of an evaluation sheet. The cardiac specialist forwards the evaluation sheet to the responsible personnel of the blinding team, who forwards the sheet to the respective investigational site and the data management of [redacted].

[redacted] will calculate the Δ QTc value. In case the QTc interval shows a prolongation of more than 500 ms during or after treatment or indicates an increase by more than 60 ms compared to baseline (ECG-1), [redacted] will inform the internal data monitoring committee and the sponsor so

that assessment of safety of the study can be done. In addition to this [redacted] will inform the responsible investigator of the respective site in case the QT interval prolonged by more than 60 ms compared to baseline value (Δ QTc > 60 ms).

If the interpretation of QTc prolongation is unclear or associated with clinically relevant arrhythmias, an expert in cardiological electrophysiology at the respective center will be involved in interpreting the respective ECGs and to define further proceeding.

8.7. Previous and concomitant disease, medication and treatment

Diseases, any medications and treatments the patients received in the last 6 months prior to study start and during the study must be recorded in the case report form (CRF). A description of the type of drug or treatment, the drug amount, duration, reason for drug administration and outcome must also be documented.

Adverse events (AEs) related to the administration of a concomitant medication or the performance of a procedure not part of the routine PCI must also be documented on the appropriate AE page of the CRF.

The use of concomitant medication that interfere with the QTc interval is not allowed.

8.8. Rescue therapy for emergencies

Excessive anticoagulation can be controlled by stopping argatroban infusion or reducing infusion dose. A specific antidote does not exist. Treatment shall be done according to symptoms and medical indication.

8.9. Continuation of treatment after the end of the clinical trial

Treatment after the PCI procedure will be according to local clinical routine.

9. Premature termination

9.1. Withdrawal of patients

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. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

9.2. Closure of trial sites

See "premature termination of trial".

9.3. Premature study termination

Both the sponsor and the principal coordinating investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the sponsor and the principal coordinating investigator will assure that adequate consideration is given to the protection of the patient's interests. The following criteria could lead to a discontinuation or early termination of the study:

- Negative benefit/risk assessment due to new information
- It is no longer ethical to continue treatment with the IMP
- It is no longer practicable to complete the trial
- The sponsor considers that the trial must be discontinued for safety reasons (e.g. after occurring of an increase in QT/QTc > 500 ms or of > 60 ms over baseline in a number of ≥ 30% patients)
- Business considerations

In case of premature study termination all collected data must be analysed and a report has to be written. The sponsor has to inform the responsible regulatory authority and the responsible ethics committee within 15 days, giving detailed reason for the premature termination.

10. Study assessments, efficacy and safety variables

10.1. Clinical and laboratory assessments

The following assessments will be collected and documented accordingly in the CRF:

Screening:

- Informed consent
- Inclusion and exclusion criteria
- Age, gender, ethnicity, height, bodyweight
- Vital signs (resting pulse rate, systolic and diastolic blood pressure measured in a sitting position)
- Information on coronary artery disease
- Pregnancy test (urine)
- Hemogram (containing leucoytes, thrombocytes, hemoglobin, hematocrit)
- Liver function profile (bilirubin, AST/SGOT, ALT/SGPT, γGT)
- Kidney function profile (serum creatinine, GFR)
- Hs-Troponin-T
- Electrolytes (Na, K, Ca)
- Coagulation status (INR, aPTT)
- 12-lead ECG-1

- Relevant medical history and current medical conditions
- Previous and concomitant medication
- Previous treatment (non-drug therapy) related to cardiac disease

Treatment:

- Duration of PCI
- Coagulation status (ACT)
- Hematocrit (only if clinically necessary)
- 12-lead ECG-2
- Information on concomitant drug treatment
- Adverse Events

Follow-up:

- Coagulation status: ACT and dTT (for assessment of argatroban plasma concentration)
- Hematocrit
- 12-lead ECG-3
- Information on concomitant treatment (drug and non-drug therapy)
- Adverse Events

10.2. Primary target variable

QTc interval:

The QT interval represents the duration of ventricular depolarization and subsequent repolarization and is measured from the beginning of the QRS complex to the end of the T wave. Reading of ECG data including the calculation of QT interval will be done automatically by use of the ECG machine Mac 5500, GE Healthcare supplemented by manual reading in any case.
Measurement of QT time will be done according to recommendations published by Goldenberg et al. [9]. This also includes tracing at 25 mm/s paper speed at 10 mm/mV amplitude for an accurate measurement of QT interval duration. In addition, QT interval will be determined as a mean value derived from the least 3-5 cardiac cycles (heart beats), and is measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. The QT measurement is made in leads II and V5 or V6, the longest value will be used [9].

Because of its inverse relationship to heart rate, measured QT interval will be routinely corrected by a formula to a less heart rate dependent value known as the QTc interval:

$$\text{Bazett's correction: } QTc = QT/RR^{0.5}$$

The RR interval is the interval between two R-waves in the ECG.

To answer the primary endpoint, QTc interval will be determined by 12-lead ECG at following time points:

- Prior to first bolus dose of argatroban (baseline ECG/ ECG-1)

- Immediately after cardiac intervention when patient is under full anticoagulation with argatroban (ECG-2)

All ECGs measurements will be forwarded to an ECG reader, a cardiac specialist, blinded to time, treatment and patient identifier. Therefore, each ECG will get a random number identifying the patient and timing of PCI.

10.3. Secondary target variables

QTc interval:

To answer the secondary endpoint, QTc interval will be determined by 12-lead ECG at following time point:

- > 8 but ≤ 28 hours after termination of infusion of argatroban maintenance dose (ECG-3)

10.4. Other variables

ACT:

Blood samples for the assessment of anticoagulation level will be obtained from patients as described in section 6.3.

Plasma samples will be obtained from patients at 5 min after completion of the initial bolus of argatroban and at 5 min after completion of every further bolus until target ACT range is reached. A final ACT measurement is planned > 8 but ≤ 28 hours after PCI. Further ACT assessments are possible but depend on clinically relevancy (e.g. in case of prolonged PCI procedure).

The final ACT measurement > 8 but ≤ 28 hours is to be conducted as part of the follow-up procedure in order to evaluate whether the pharmacodynamic effect of argatroban faded off completely. This status is indicated by an ACT value of ≤ 160 s. If clinically indicated, further ACT assessments can take place.

10.5. Bleedings

The incidence of hemorrhagic events during the PCI must be categorized according to the definition of CABG-related bleeding [10]:

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision

Type 4	CABG-related bleeding within 48 hours
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

10.6. Adverse events and adverse drug reactions

The summary of product characteristics (SmPC) will be used as reference document for study medication and will be provided to the investigators.

It is the responsibility of investigator(s) to report all AEs in the CRF. Any serious adverse event (SAE) must be reported to the sponsor within one working day.

10.6.1. Adverse event (AE)

An AE is any untoward medical occurrence in a patient administered an IMP. There does not necessarily have to be a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or ECG finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen during a study are to be reported as AEs. They can become SAEs if they fulfill one of the seriousness criteria described in section 10.6.2.
All AEs encountered during the clinical study will be reported on the AE page of the CRF. Reporting of new AEs starts at the beginning of the study (date of treatment visit) and ends at study termination (after completion of ECG-3 measurement).

AEs of special interest are cardiac (e.g. arrhythmic) events. For that reason, each abnormal ECG finding (e.g. morphological abnormality like prolonged QT/QTc interval) must be handled and respectively documented as AE. An evaluated QT/QTc interval is categorized as "prolonged" if the following limit is reached: **Absolute QTc interval prolongation: QTc interval > 450 ms**.

Severity of AEs will be graded 1 through 3 and reported in detail as indicated on the CRF:

- Grade 1, Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2, Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate daily activity.
- Grade 3, Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, Inability to work or perform normal daily activity.

Relationship of the AE to treatment should also be assessed. Description of scales can be found in section 10.6.5.

10.6.2. Serious adverse events (SAE) and serious adverse drug reactions (SADR)

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence that at any dose

- results in death

- is life-threatening at the time of the event
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect
- is medically important condition

Inpatient hospitalization is defined as any stay in hospital on the part of a patient that includes at least one night (midnight to 06:00). Scheduled admission to hospital before first admission of IMP are not SAEs, but must be documented in the proper manner in patient's medical records and CRF.

10.6.3. Unexpected adverse drug reaction (UADR)

An unexpected ADR is an ADR whose nature or severity is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the Summary of Product Characteristics (SmPC, Information Sheet for Health Professionals [Fachinformation in Germany]).

10.6.4. Suspected unexpected serious adverse reactions (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is an AE whose nature or severity is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

10.6.5. Causal relationship between adverse event and IMP

The causality will be initially assessed by the investigator. For causality assessment, a binary grading will be used:

- Related/ "*Reasonable Possibility*": Any AE for which there is a reasonable possibility that the drug caused the AE. A *reasonable possibility* means there a facts (evidences) or arguments to suggest a causal relationship, regardless of whether there are less or more degrees of certainty between the drug and the AE.
- Not Related/ "*No Reasonable Possibility*": Any AE for which there is not a reasonable possibility that the drug caused the AE.

10.6.6. Documentation and follow-up of adverse events

Documentation of AEs will begin with study start (date of treatment visit). All AEs will be documented in the CRF including following information:

- AE description
- Severity
- Causal relationship with IMP / study treatment
- Expectancy
- Seriousness

- Action taken
- Outcome
- Date of onset and resolution

Regardless of whether a causal relationship between the AE and the IMP is suspected, patients who develop AEs must be monitored until all symptoms have subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the patient has died or the study was terminated for the patient concerned.

All AEs and SAEs, including those that are ongoing at date of study termination, will be followed up until resolution or until the investigator decides that no further follow-up is necessary. Anyhow, ongoing AEs will be followed up within a period of 28 days after study termination at the latest.

Treatment of AEs is at the discretion of the investigator and should follow the standards of medical care at the investigator's institution.

10.6.7. Reporting of serious adverse events and pregnancy

The investigator and other center personnel must inform the appropriate Mitsubishi Tanabe representatives of any SAE and pregnancy that occurs during the study within 24 hours of being made aware of such. Follow-up information on SAEs must also be reported by the investigator within the same time frame.

All correspondence on pharmacovigilance and information on SAEs as well as pregnancies should be addressed to:

Mitsubishi Tanabe Pharma Europe Ltd.
Safety Department
Dashwood House
69 Old Broad Street
London EC2M 1QS
United Kingdom

[redacted]

10.6.8. Assessment of event by sponsor

All cases of suspected SAEs are assessed by the sponsor and the investigator with regard to seriousness, causality and expectedness.

10.6.9. Notification of ethics committee and competent supreme federal authority

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor or investigator to the competent supreme federal authority and the ethics committee.

Fatal and life-threatening SUSARs

The competent supreme federal authority and the responsible ethics committee must be informed of all fatal or life-threatening SUSARs by the sponsor or investigator. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the

competent supreme federal authority and the ethics committee within a time-span of another 8 days. Furthermore, if a patient dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

SUSARs that are not fatal or life-threatening

The competent supreme federal authority and the ethics committee responsible will be informed without delay by the sponsor or investigator of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

10.6.10. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the sponsor or investigator will inform the competent supreme federal authority and the ethics committee responsible of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. Especially:

- Individual reports of expected serious ADRs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SADRs
- Factors emerging in connection with trial conduct or the development of the IMP that may affect the safety of persons concerned.

10.6.11. Informing the investigators

The investigator will also inform his substitute of all SAEs.

11. Quality management

11.1. Risk management

In order to secure the quality of study conduct and study data, respective quality assurance measures are implemented.

Quality of Study Conduct

The conduct of the study is aiming to treat study patients at the highest possible level of safety and efficacy. SAICoDis specifically addresses the question whether the infusion of Argatroban may be associated with the risk of prolongation of the QTc interval. Therefore, internal data monitoring will be performed by reviewing the results of ECG evaluation. Each study center nominates an ECG expert if specific advices are required.

Antithrombotic Prophylaxis

Since the invasive PCI procedure, particularly in combination with stent implantation is associated with increased procoagulant risk, patients undergoing PCI receive both antiplatelet and anticoagulant therapy. The antiplatelet agent(s) are given pre- and post-interventionally, while the

anticoagulant drug is usually applied only during the intervention. Argatroban shows a shorter half-life time compared to standard anticoagulant unfractionated heparin. This difference of pharmacokinetics has been addressed by adjusting the study protocol in such a way that intervention procedure is only to be initiated, when either antiplatelet therapy has reached already a steady-state level, or a bolus of the antiplatelet drug is administered before start of PCI.
This aspect is subject of continuous training of study physicians.

Consistency ECG and laboratory data

Collected ECG data and Argatroban plasma levels, each of which are assessed at one single site in order to secure highest level of consistency.

The ECG records are pseudonymized so that the ECG evaluator is blinded for patient-ID and time of ECG recording. A patient identifier is assigned to each ECG by CRO to assemble the 3 ECG sets of each patient in relationship to time of recording.

Personal Data Protection

The DSGVO and the respective Data Protection Policy of the sponsor apply to all patient data at all times. All staff of study centers, CRO, and sponsor involved in SAICoDis project are obliged to observe the DSGVO. The privacy of all collected patient data is secured by omitting any information on CRFs which may allow an identification of the individual. The data set related to a screened / treated study patient are characterized by a specific patient number assigned exclusively to an individual patient.

11.2. Data quality assurance

11.2.1. Monitoring

All trial site will be monitored to ensure the quality of the data collected. Monitoring will be made for study initiation, during the study and for study closure to ensure that all aspects of the protocol are followed. The objectives of the monitoring procedures are to ensure that patient's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The investigator agrees that a monitor regularly visits the trial site and assures that this monitor will receive appropriate support in activities at the trial site. The declaration of informed consent (see Section 14.4) includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare CRFs with patient's medical records (doctor's notes, ECGs, laboratory printouts etc.). The investigator must allow the monitor access to all necessary documentation for trial-related monitoring. Aims of these monitoring visits are as follows:

- To check the declarations of informed consent
- To monitor patient safety (occurrence and documentation/reporting of AEs and SAEs)
- To check the completeness and accuracy of entries on the CRFs
- To validate entries on the CRFs with source documents (source data verification, SDV),
- To perform drug accountability checks
- To evaluate the progress of the trial

- To evaluate compliance with the trial protocol
- To assess whether the trial is being performed according to GCP at the trial site
- To discuss with the investigator aspects of trial conduct and any deficiencies found

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems.

11.2.2. Audits

Authorized representatives of the sponsor or a regulatory authority may visit the trial site to perform audits or inspections, including source data verification. The aim of an audit is to verify validity, accuracy and completeness of data, to establish credibility of the clinical trial, and to check whether the patient's rights and safety are being maintained. The purpose of a Mitsubishi Tanabe audit is to determine that data were recorded, analysed and accurately reported according to the protocol, the principles of GCP, the ICH guidelines and any applicable regulatory requirements. The sponsor may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, CRFs, patients' medical records, drug accountability documentation, and trial-related correspondence).

Sponsor and trial site agree to support auditors and inspections by competent authorities at all times and to allow persons charged with these duties access to the necessary original documentation.

All persons conducting audits pledge to keep all patient data and other trial data confidential.

12. Data Management

Data management will be performed according to the determinations within the data management plan. The data management plan will describe in greater detail the methods used to collect, check and process clinical data. It will include a description of the plausibility and consistency tests that must be run during data processing as well as rules defining how to deal with any discrepancies.

For computerized data entry and data analyses standardized procedures will be used. All data will be entered double and independently by different persons in a validated study data base and checked for discrepancies.

Before data can be entered in the study data base all data are checked for correctness, plausibility and completeness. Additionally, these checks will be performed during and after data entry in the data base.

The data manager will contact the respective study center in writing, in order to resolve any occurring discrepancy. Investigators should answer queries in a timely manner.

Statistical analysis will be performed only after the study data base has been closed and declared as „Clean File ".

12.1. Study documentation, CRFs and record keeping

12.1.1. Investigator's file / retention of documents

Investigators must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: Investigator's study file and patient data.
The investigator's study file will contain all essential documents: the protocol/amendments, CRF and query forms, patient information and informed consent form, ethics committee and federal regulatory authority approval, notification of the federal regulatory authority and competent regional authorities, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.
Patient data include patient hospital/clinic records (medical reports, OP reports appointment book, medical records, pathology and laboratory reports, ECG, EEG, X-ray, etc.), signed informed consent forms, patient screening and identification forms.
The investigator must keep these two categories of documents on file for at least 15 years (or more as legally required) after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

12.1.2. Source documents and background data

On request, the investigator shall supply the sponsor with any required background data from the study documentation or clinic records. This is particularly important when CRF entries are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, providing that patient confidentiality is protected. According to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

12.1.3. Case report form

For each patient enrolled, the CRF must be completed and signed by the principal investigator or authorized delegate from the site staff. These signatures serve to attest that the information contained within the CRFs is complete and true. At all times, the principal investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the physician's patient records maintained at the site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital's or the physician's chart, the information collected on the CRFs must match those charts. Corrections shall be signed and dated and the originally entered data shall stay visible.

12.1.4. Audits and inspections

This study may be audited by the sponsor, any person authorized by the sponsor or the competent health authority in order to determine the authenticity of the recorded data and compliance with the

study protocol. The investigator should understand that source documents for this trial should be made available to qualified personnel from sponsor/monitors/auditor/health authority inspectors after appropriate notification. These documents are needed for source data verification and proper review of the study progress. CRF data must be verified by direct inspection of source documents. The investigator agrees to comply with sponsors and regulatory authority requirements regarding auditing of the study. All material used in clinical studies are subjected to quality control.

13. Sample size calculation and statistical methods

13.1. Sample size calculation

A one-sided one sample t-test with a significance level of 5% will be used to test the primary hypothesis of this study that QTc will not increase more than 10 ms under argatroban. Table 1 depicts the power of the test with 45 evaluable patients for varying population means Δ QTc.

Δ QTc in population	Power	β
0	> 0.999	< 0.001
1	> 0.999	< 0.001
2	> 0.999	< 0.001
3	0.999	0.001
4	0.990	0.010
5	0.951	0.049
6	0.841	0.159
7	0.632	0.368
8	0.373	0.627

Table 1: Power of test (one-sided one sample t-test, alpha=5%, n=45 evaluable patients)

Up to a population mean of Δ QTc = 6 the power of the test will be adequate, i.e. > 0.8. To account for potential dropouts at least 50 patients will be enrolled into the study, assuming a dropout rate of about 10%.

13.2. Randomisation

Not applicable.

13.3. Statistical methods

13.3.1. Study population definitions

Each patient will be assigned to appropriate analysis populations for statistical analysis. The different analysis populations are:

- All enrolled population

All patients enrolled into the study regardless if they were treated or not.

- Intention to treat population (ITT population), safety population:

All patients who took at least one dose of treatment.

- Per protocol population (PP population):

All patients in the ITT population fulfilling the criteria for inclusion, none of the exclusion criteria and also complied to study design.

13.3.2. Disposition

Description of patients' disposition will be based on the all enrolled population. The number of patients enrolled and treated or not treated, will be depicted total and by center. A listing will be provided of all patients who discontinued treatment or study, including the reason for withdrawal.

This section will give details about the number of patients adhering to the inclusion criteria of the protocol and the number of patients fulfilling exclusion criteria. A listing will be provided of all patients who were excluded from each analysis population.

13.3.3. Demographic characteristics

Patients' continuous demographic and baseline variables will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while categorical variables will be summarized using frequency tabulations. Individual patient listings will be provided.

13.3.4. Study drug

For argatroban dosage, statistics (mean, standard deviation median, minimum and maximum) will be provided for the dose level achieved during bolus, prolonged argatroban infusion and the cumulative dose. Duration of exposure will be similarly outlined with a summary of dosing interruptions and reductions.

13.3.5. Safety evaluation

Description of safety will be based on the ITT population. The primary variable will also be analysed by the PP population.

13.3.5.1. QTc - Statistical hypothesis (primary variable)

Following measurements of QTc will be made for each patient:

- Prior to first bolus dose of argatroban: QTc_1
- immediately after cardiac intervention in a status of full anticoagulation with argatroban: QTc_2
- > 8 but ≤ 28 hours after termination of prolonged argatroban infusion: QTc_3

The statistical hypothesis of this study refers to the difference QTc_2 minus QTc_1 = Δ QTc:

H_0: Δ QTc > 10 ms

H_A: Δ QTc ≤ 10 ms.

H_0 will be tested by a one-sided one sample t-test with a significance level of alpha=5%. Data from all patients with measurements QTc_1 and QTc_2 will be included in the analysis of Δ QTc.

Additionally, Δ QTc as well as QTc_1 and QTc_2 will be described by descriptive statistics (mean, standard deviation, median, minimum, maximum, and 95%-confidence interval). An individual patient listing will be provided with QTc_1, QTc_2, Δ QTc, QTc_3 and the difference QTc_3 minus QTc_1.

The analysis of the primary variable will be based on the ITT sample. It will be repeated for the PP sample. The study report will contain a statement about difference in study results between the ITT and PP sample.

13.3.5.2. Secondary target variables

- Mean difference in QTc interval between ECG-3 and ECG-1.

The difference QTc_3 minus QTc_1 will be defined by descriptive statistics. If the 95%-confidence interval includes the value 0, a return of QTc-values to baseline values will be stated.

- Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-2.
- Proportion of patients with a prolongation of QTc interval to > 500 ms at ECG-3.
- Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-2 compared to ECG-1.
- Proportion of patients with a prolongation of QTc interval of > 60 ms at ECG-3 compared to ECG-1.

One-sided 95%-Pearson-Clopper confidence limits will be computed for those proportions.

- Incidence of haemorrhagic events according to the definition of CABG-related bleeding.

A two-sided 95%-Pearson-Clopper confidence limit will be computed for the proportion of patients with haemorrhagic events.

13.3.5.3. Adverse events

Adverse events will be classified using the MedDRA (Medical Dictionary for Regulatory Activities) classification system. The frequency of AEs will be tabulated by preferred term and body system. Statistical analysis will not take into account MedDRA low level terms and start at preferred term level. In the by-subject analysis, a patient having the same preferred term more than once will be counted only once.

In addition to an analysis of all AEs, AEs with a causal relation to argatroban treatment will be analysed separately.

13.3.6. Interim analysis

No interim analysis is planned.

13.3.7. Subgroup analysis

Study data will be analysed split by sex of patients and by center.

13.3.8. Missing values

Missing data in other variables caused by patients who dropped out of the study/ other reasons will not be replaced by any methods of imputation. Instead, frequency of missing values will be presented.

13.3.9. Software used for analysis

Data processing and statistical analysis will be executed using the program system SAS (version 9.4 or later).

14. Ethical and regulatory aspects

14.1. Ethical basis for the clinical trial, Legislation and guidelines used for preparation

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finnland, 1964 and later revision (October 2013, 64th General Assembly of the World Medical Association, Fortaleza, Brazil [11]).

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) [12] and applicable legislation (especially the Federal Drug Law [AMG] [13] and the GCP-V [8]). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from patients, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, patients' medical records (source documents), documentation and reporting of AEs, preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the competent federal authorities and authorized representatives of the sponsor have the right to review trial documentation and patients' medical records at any time.

14.2. Independent ethics committee (IEC)

The clinical trial will not be started before approval of the competent ethics committee. It is the responsibility of the investigator to obtain approval of the study protocol/amendments from the IEC according to the local requirements. The lead ethics committee in this clinical trial is [redacted].

14.3. Notification of authorities, approval and registration

Before start of the clinical trial, all necessary documentation will be submitted to the competent supreme federal authority for approval (Federal Institute for Drugs and Medical Products, Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]).

14.4. Obtaining informed consent from patients

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, only after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study according to § 40 Abs. 2 and § 40 Abs. 2a AMG. As part of that process, the investigator hands out the following complete documents to the patient: patient information, informed consent form, insurance policy and conditions of insurance.

Written informed consent must be obtained before any study-specific procedures are performed. It must be emphasized that patients are completely free to refuse to enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator.

By signing the consent form, the patient agrees with the "Unwiderrufliche datenschutzrechtliche Einwilligung" according to § 40 Abs. 2a AMG. The patient also agrees to allow the monitor/auditor/health authorities to verify the collected patient data by comparing it to the patient's original medical records for the purpose of source data verification. The informed consent form personally signed and dated by the patient must be kept on file by the investigator(s), and documented in the CRF and the patient's medical records. The investigator confirms that the written informed consent was obtained.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give written informed consent to continue in the study.

If family practitioners are informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

14.5. Insurance of patients

All enrolled patients are insured in accordance with § 40 AMG under the insurance contract with the insurance company [redacted]. Headquarters, policy number and telephone and fax number will be included in the patient information sheet.

14.6. Data protection

The informed consent form will incorporate wording that complies with relevant data protection and privacy legislation. In accordance to this wording, patients will authorize collection, use and disclosure of their study data by the investigator and persons in need of this information for the purpose of the study.

The provisions of data protection legislation must be observed. Investigator, sponsor and his designee must assure that according to the standards of data protection law, all data obtained in the study must be treated with discretion in order to guarantee the rights of the patient's privacy. CRFs or other documents should be submitted to the sponsor in a pseudonymized manner. The investigator should keep a patient identification log showing codes and names.

Patients will be informed that evaluated data during this study will be electronically stored and handed over to the data management for data entry in a pseudonymized form. Patients who do not agree that information may be passed on in this way may not be enrolled into the trial.

15. Use of trial findings and publication

15.1. Reports

15.1.1. Interim reports

No interim analysis planned.

15.1.2. Final report

The competent authority and ethics committee will be informed within 90 days that the trial has officially ended.

Within one year after trial completion, the competent federal authority and the ethics committee will be supplied with a summary of the final report on the clinical trial containing the principle results.

15.2. Publication

It is planned to publish trial results in mutual agreement with the investigator in a scientific journal. Publication of trial results en bloc is intended. Any publication will take account the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997;277:927-34]).

Any published data will observe data protection legislation covering patient and investigators.

16. Amendments to the trial protocol

In the interest of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases however, changes may be made to the trial protocol. Such changes can only be done if agreed by the sponsor, sponsor's representative, investigator, biometrician and all authors of this trial protocol. Any changes to trial procedures must be declared in writing and must be documented along with reasons. It needs to be signed by all authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions comprise amendments made to avoid immediate dangers.

17. Literatur

1 *Cruz-Gonzalez I, Sanchez-Ledesma M, Osakabe M et al.* What is the optimal anticoagulation level with argatroban during percutaneous coronary intervention? Blood coagulation & fibrinolysis an international journal in haemostasis and thrombosis 2008; 19(5): 401–404

2 *Jang I-K, Hursting MJ.* When heparins promote thrombosis: review of heparin-induced thrombocytopenia. Circulation 2005; 111(20): 2671–2683

3 *Lewis BE, Matthai WH, Cohen M et al.* Argatroban anticoagulation during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. Catheterization and cardiovascular interventions official journal of the Society for Cardiac Angiography & Interventions 2002; 57(2): 177–184

4 *Jang I-K, Lewis BE, Matthai WH, Kleiman NS.* Argatroban anticoagulation in conjunction with glycoprotein IIb/IIIa inhibition in patients undergoing percutaneous coronary intervention: an open-label, nonrandomized pilot study. Journal of thrombosis and thrombolysis 2004; 18(1): 31–37

5 *Rössig L, Genth-Zotz S, Rau M et al.* Argatroban for elective percutaneous coronary intervention: the ARG-E04 multi-center study. International journal of cardiology 2011; 148(2): 214–219

6 *Heist EK, Ruskin JN.* Drug-induced proarrhythmia and use of QTc-prolonging agents: clues for clinicians. Heart rhythm the official journal of the Heart Rhythm Society 2005; 2(2 Suppl): S1-8

7 2018 ESC/EACTS Guidelines onmyocardial revascularization

8 Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung, GCP-V) 2012

9 *Goldenberg I, Moss AJ, Zareba W.* QT interval: how to measure it and what is "normal". Journal of cardiovascular electrophysiology 2006; 17(3): 333–336

10 *Mehran R, Rao SV, Bhatt DL et al.* Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123(23): 2736–2747

11 WMA Deklaration von Helsinki-Ethische Grundsätze für die medizinische Forschung am Menschen 2013

12 *www.ich.org*

13 Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz, AMG), 16. Novelle; 2013 2013