REVACEPT, A NOVEL INHIBITOR OF PLATELET ADHESION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE UNDERGOING ELECTIVE PERCUTANEOUS CORONARY INTERVENTIONS: A PHASE II, MULTICENTRE, RANDOMISED, DOSE-FINDING, DOUBLE-BLIND AND PLACEBO-CONTROLLED STUDY.

EudraCT Number: **2015-000686-32**

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Investigator Agreement Page

By my signature below, I hereby attest that I have read, discussed and understood the background information concerning the investigational product. I have read and discussed this Protocol and agree to carry out the trial as set out therein. I agree that the trial shall be carried out according to ICH Good Clinical Practice (GCP) standards and all applicable regulatory requirements. I accept my obligations relating to the principles that have their origin in the Declaration of Helsinki and specifically to Independent Ethics Committee (IEC), Informed Consent, and also my obligations to Deutsches Herzzentrum München, or contracted representatives, as far as safety reporting, providing data, allowing monitoring, auditing, inspection by domestic and foreign Regulatory Authorities and quality control visits are concerned.

Institution: _____

Principal Investigator:

Name: _____

Date:_____ Signature: _____

Deputy Principal Investigator:

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Date:_____ Signature: _____

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SYNOPSIS

Name of Sponsor: Deutsches Herzzentrum München Sponsor Representative: Prof. Dr. med. Adnan Kastrati Lazarettstraße 36 D-80636 Munich Germany Tel.: +49 (0)89 1218 4578	Coordinating Investigator: Prof. Dr. med. Adnan Kastrati Deutsches Herzzentrum München Klinik für Herz- und Kreislauferkrankungen Lazarettstraße 36 D-80636 Munich Germany Co-Coordinating Investigator: Prof. Dr. med. Steffen Massberg Klinikum der Universität München Medizinische Klinik und Poliklinik I Marchioninistraße 15 D-81377 Munich Germany
Title of study: REVACEPT, A NOVEL INHIBITOR OF PLATELET ADHESION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE UNDERGOING ELECTIVE PERCUTANEOUS CORONARY INTERVENTIONS: A PHASE II, MULTICENTRE, RANDOMISED, DOSE-FINDING, DOUBLE-BLIND AND PLACEBO-CONTROLLED STUDY	
Protocol identification (code or number): Revacept/CAD/02	

OBJECTIVES

The main objective is to evaluate the efficacy and safety of treatment with 2 doses (80 and 160 mg) of Revacept versus placebo. Periprocedural antithrombotic therapy composed of clopidogrel, ASA and heparin (or bivalirudin) will be administered based on local practice and current guidelines. The treatment effect will be assessed using the following endpoints:

- Primary endpoint of the study

  A composite endpoint of death or myocardial injury (defined as increase in cardiac biomarker – high sensitivity cardiac troponin T of at least 5 times the upper limit of norm (ULN)) within 48 hours from randomisation.

- Secondary endpoints

- Peak high-sensitivity troponin T level within 48 hours from randomisation

to be evaluated within 30 days after randomisation and will include:

- All-cause mortality
- Myocardial infarction
- PCI-related (type 4a) myocardial infarction
- Definite stent thrombosis
- Urgent coronary revascularization
- Stroke
- Bleeding complication class 2 or higher according to Bleeding Academic Research Consortium (BARC) criteria (safety endpoint)

Methodology:

Multicentre, randomised, dose-finding, double-blind, 3-arm, placebo controlled phase II study.

Blinded evaluation of anti-ischemic efficacy and safety endpoints.

Treatment Regime:

Patients with coronary artery disease scheduled for elective PCI receive periprocedural antithrombotic therapy composed of clopidogrel, ASA and heparin (or bivalirudin) based on local practice and current guidelines. Revacept or placebo infusion will be started as soon as possible after the decision to perform PCI but prior to the start of the PCI procedure (guidewire passage).

Treatment Groups:

332 patients currently receiving standard therapy plus one intravenous infusion of:

- Placebo (90 patients)
- 80 mg Revacept (121 patients)
- 160 mg Revacept (121 patients)

Inclusion and exclusion criteria:

Inclusion criteria:

- Signed written informed consent
- Men and women >18 years of age
- Diagnosis: Clinically stable coronary artery disease
- Angiographic evidence of coronary artery disease
- Indication for PCI

Exclusion criteria:

- WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for up to 4 weeks after receiving investigational product.
- Women who are pregnant or breastfeeding or are planning pregnancy during course of trial
- Women with a positive pregnancy test on enrolment or prior to investigational product administration.
- Patients with elevated high sensitivity cardiac troponin T levels at screening
- Patients receiving antithrombotic therapy with Prasugrel or Ticagrelor within 7 days prior to randomisation
- History of hypersensitivity, contraindication or serious adverse reaction to any component of the study drug (GPVI-Fc, sucrose, mannitol), acetylsalicylic acid or clopidogrel
- History of bleeding diathesis or active bleeding within the last 30 days
- Recent intracerebral haemorrhage or trauma within the last 3 months
- Thrombocytopenia (platelet count <30000/mm^3) at screening
- Sustained hypertension (systolic BP >179mmHg or diastolic BP >109mmHg) at screening
- Renal failure (estimated glomerular filtration rate< 30ml/min and/or dialysis)
- Severe systemic disease, such as known malignancies or other comorbid conditions with life expectancy less than one year that may result in protocol non-compliance
- Unable to provide informed consent (e.g. severe dementia, or psychosis)
- Current severe liver dysfunction (transaminase level >5-fold the upper normal range limit)
- Patients with an indication for anticoagulant therapy
- Participation in any other clinical interventional trial (drug/device) within less than 30 days prior to screening
- Any other contraindication to perform PCI
- Any planned additional PCI or surgery within 30 days after randomisation
- Suspected poor capability to follow instructions and cooperate

- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness (e.g. infectious disease)

Trial duration per subject:

Trial duration per subject will be 30 days.

Duration of study:

The total duration of this study is planned until 332 patients are recruited.
Start date: 14 Nov 2017
Planned recruiting period: 29 months
Planned LPFV: Feb 2020
Planned LPLV: Mar 2020

Statistical methods:

Two ordered hypotheses will be tested. The first hypothesis to test is that whether there is a significant difference in the primary endpoint among the 3 study groups in favor of Revacept treatment. Sample size calculation was based on the following assumptions: incidence of the primary endpoint of 25% in the placebo group (as shown by a recent analysis of 2000 patients meeting study criteria from the database of the Deutsches Herzzentrum München) and 8% and 17% in the higher and lower Revacept doses groups, respectively (corresponding to an overall 50% relative risk reduction in the combined Revacept doses groups vs. placebo), 2-sided alpha-level of 0.05 and power of 80%. These assumptions led to a total sample size of 270 patients, 90 patients in each of the 3 study groups (calculated with nQuery). Because it is a short-term study encompassing only 48 hours from the index procedure, no drop-outs are expected.
If there is a statistically significant difference between the three study groups, a comparison between the 2 Revacept doses groups will follow in a second step. One way to select the better of the two Revacept groups is to select the dose with the larger response rate (Simon et al. 1985). The other way is to increase the type I error rate at α=20% (Rubinstein et al. 2005). We will apply the latter approach. Concerning the second hypothesis, the comparison of the study doses, based on the given sample size in order to detect a difference between 8% and 17% with a power of 80% using type I error rate of 20%, 121 patients per group (in total 242 patients) are needed. This means that we have to enroll a total of 332 patients in this study (90 patients in placebo group and 121 patients in each of the Revacept doses groups). In the case that the study meets the first but not the second hypothesis in statistical terms, an overall evaluation of both efficacy and safety findings will be performed. In general, comparability of the results will be in support of the lower dosis to be used in subsequent trials involving this category of patients.

The comparison of characteristics between the 3 groups will be performed by the Chi-square test or Fisher's exact test as appropriate. The continuous data will be compared by the use of the Kruskal-Wallis rank-sum test. Analysis of the primary and secondary efficacy endpoints will be performed according to the intention to treat principle, analysis of safety endpoints according to modified intention to treat principle. The treatment effect across the 3 groups will be assessed by the test for trend using the logistic regression by assigning 0 to the placebo group, 1 to the lower-dose Revacept group and 2 to the higher-dose Revacept group. The logistic model will account for stratification according to the participating centers. The use of a

logistic model that accounts for stratification factors is in accordance with “Statistical Principles for Clinical Trials” ICH Topic E9. If there is a significant difference between the three groups the two Revacept groups will be compared by using the chi-square test.

LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BfArM	Bundesministerium für Arzneimittel und Medizinprodukte
BMBF	Bundesministerium für Bildung und Forschung
BP	Blood pressure
bpm	beats per minute
CAD	Coronary Artery Disease
eCRF	electronic Case Report Form
CRP	C-reactive protein
CV	Curriculum Vitae
D or d	Day
DQF	Data Query Form
ECG	Electrocardiogram
EDS	Electronic Data Capture System
ESR	Expedited Safety Report
EU	European Union
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
eGFR	Estimated Glomerular Filtration Rate
GP	General Practitioner
Hr or hrs	hour or hours
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalisation ratio
IRA	Infarct-Related Artery
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
ITT	intention-to-treat
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MTD	maximum tolerated dose
NA	Not applicable
NAV	Not available
ND	Not done
OAC	Oral Anti-Coagulant
PCI	Percutaneous Coronary Intervention
PP	Per Protocol
PPP	Platelet Poor Plasma
PRP	Platelet Rich Plasma
PT	Prothrombin time
QCA	Quantitative Coronary Angiography
RBC	Red Blood Cell
RRR	Relative Risk Reduction
SAE	Serious adverse event
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Event
TAT	Thrombin-Antithrombin III
tmax	Time to Cmax
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

1. STUDY ADMINISTRATIVE STRUCTURE

1.1. Sponsor Details

The sponsor of the investigation is:

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1.2. Coordinating Investigator

The Coordinating Investigator for the investigation is:

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1.3. Steering Committee

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Klinikum rechts der Isar München
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Klinik und Poliklinik für Innere Medizin

PD Dr. med. Stefanie Schüpke
Deutsches Herzzentrum München
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1.4. Supporter Details

The study is supported financially by:

advanceCOR GmbH
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and

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1.5. Manufacturer

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1.6. Coordinating Research Center

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1.7. Monitoring

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1.8. Biometry/Statistics

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1.9. Data Management

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1.10. Pharmacovigilance

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1.11. Core Laboratory

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2. INTRODUCTION AND STUDY RATIONALE

Although antiplatelet agents reduce the risk of ischemic/thrombotic complications in the setting of medical or invasive therapy of ischemic heart disease, their use invariably incurs the risk of potentially life-threatening bleeding. It is therefore highly desirable to develop novel therapeutic strategies that selectively inhibit thrombogenesis at the site of vascular stenosis or vascular intervention, whilst not compromising systemic haemostasis.

Such selectivity can be achieved by targeting structures that differ between healthy and atherosclerotic vasculature. Collagen is an important component of the extracellular matrix of arterial walls and thus shielded from the blood stream by the vascular endothelium under normal conditions. Upon vascular injury or atherosclerotic plaque rupture, however, collagen becomes increasingly exposed to the arterial lumen. A crucial step in platelet adhesion is binding to glycoprotein VI (GPVI), the endogenous platelet collagen receptor (Nieswandt et al., 2003). Remarkable potential to prevent local thrombosis without jeopardizing systemic platelet function and coagulation lies in inhibiting GPVI-collagen interaction rather than directly inhibiting thrombocytes. This clinical trial wants to investigate this innovative and highly specific approach to prevent local thrombosis while the normal thrombocyte function (primary haemostasis) is not affected. It is in striking contrast to other antiplatelet regimens and might provide a better benefit-risk ratio (Ungerer and Münch 2013). Scientists from Ludwig-Maximilians-University (LMU) and Technical University (TU) Munich contributed tremendously in understanding the GPVI-collagen interaction. After a long way of fundamental research they developed a soluble GPVI-Fc dimer, called Revacept (Schönberger et al., 2012, Ungerer et al., 2011, Ungerer et al., 2013, Goebel et al. 2013, Bültmann et al. 2010; Schönberger et al. 2008, Massberg et al. 2004).

Revacept is a protein that is made up of an Fc fragment ("fragment crystallisable") fused to the GPVI receptor (an endogenous platelet collagen receptor). Consequently, Revacept binds to its ligand (collagen) on atherosclerotic plaques preventing circulating thrombocytes from binding to collagen exposed by the injured plaque, most importantly not impairing general thrombocyte activity in animal models (Massberg et al., 2004, Bültmann et al., 2010). When arterial lesions were induced in mice models of atherosclerosis, Revacept was effective at preventing platelet adhesion and thrombus formation at these sites without affecting bleeding time. After carotid lesions in mice, GPVI-Fc prevents arterial thrombosis, as assessed by intravital microscopy (Massberg et al., 2004), and reduces stroke volumes (Goebel et al., 2013). After coronary ligation in mice, infarct size is reduced (Schönberger et al., 2012) by Revacept. Safety assessment showed no increased bleeding risk even in combined triple antiplatelet or anticoagulant therapy (Ungerer et al., 2013). Furthermore, Revacept is characterised by a promising pharmacovigilance profile with no toxicities or signs of aberrant immune activation detected in preclinical animal studies even after repeated dosing (Göbel et al., 2013, Ungerer et al., 2013).

Thus, blocking of GPVI-dependent pathways by interfering in vascular collagen sites is commonly seen as an attractive target for an anti-platelet therapy of acute atherosclerotic diseases, such as myocardial infarction or stroke.

Following these encouraging preclinical studies, safety and tolerability of Revacept was investigated in a first-in-man study (Ungerer et al., 2011). In a phase I clinical trial, human volunteers received a single intravenous dose of Revacept ranging between 10-160 mg. All

investigated doses were well tolerated and no drug-related side effects occurred. Moreover, no anti-Revacept antibodies were produced and favourable pharmacokinetic and pharmacodynamic profiles were observed. In summary, results from both preclinical studies and the phase I clinical trial constitute a solid basis for proceeding to a clinical trial in the target patient population. A first phase II study Eudra-CT 2011-001006-10 (http://www.clinicaltrials.gov/ct2/show/ NCT01645306) currently investigates the use of Revacept in patients with symptomatic stenoses of the internal carotid artery, studying its impact on the occurrence of microemboli which enter the cerebral circulation, thereby potentially producing a symptomatic clinical event. They are detected by transcranial doppler (TCD) as microembolic signals (MES) (Ringelstein et al. 1998, Markus et al., 2005). Several studies have demonstrated that the incidence of MES is a potent prognostic factor for prediction of future strokes and TIAs in patients with systematic stenosis, i.e. the risk being 8 to 31 fold higher for MES positive patients than for MES negative patients (Valton et al., 1998, Molloy et al., 1999, Siebler et al., 1995).

This second phase II study intends to investigate the use of Revacept for the first time in patients with stable coronary artery disease undergoing PCI. The use of Revacept might provide a better benefit-risk ratio than existing antiplatelet therapies or novel approaches in clinical development (Ungerer and Münch 2013). In the present study a special emphasis was put on peri-procedural bleeding complications which will be identified and scaled by the BARC criteria which have been recently validated (Ndrepepa et al., 2012).

Dose selection rationale

Detailed background information on preclinical pharmacology, pharmacokinetics, toxicology and on the phase I clinical study of Revacept is provided in the Investigator Brochure. When 10 – 160 mg Revacept were administered during a phase I clinical trial including 30 patients, maximal pharmacodynamic effects were measured ex vivo, starting at 40 mg, and no drug-related adverse events occurred (Ungerer et al. Circulation 2011). Pharmacokinetic studies demonstrated that the area under the curve and maximum concentration proportionally increased with higher dose levels. Although five different doses have been evaluated in the first in man study, the optimal Revacept dose in patients with CAD still remains undefined because the phase I trial included only healthy volunteers. The maximum inhibition of collagen-induced aggregation after 2 hours was best in the 80 and 160 mg dose groups, thus these two doses have been chosen. A maximum dose of 160 mg has been considered sufficient as both pharmacokinetic and pharmacodynamic results reached maximum effects (complete inhibition of collagen-mediated platelet aggregation) with no further inhibitory effect by further dose escalation. Regarding safety data retrieved from the ongoing Revacept study in patients with stroke or TIA (Eudra-CT-Nr.: 2011-001006-10), no bleeding in correlation to dose was observed. Due to this good safety profile and for efficacy reasons higher dose (80 mg and 160 mg) was selected for this second phase II study.

Overall risk/benefit assessment

Revacept is a novel therapeutic agent that potently inhibits platelet aggregation at the site of atherosclerotic plaques without compromising systemic coagulation in animal models and healthy volunteers. No toxicities were observed during preclinical studies and no adverse reactions were observed when Revacept was administered to healthy human volunteers.

Consequently, safety concerns are limited to adverse reactions specific to the target patient population and rare side effects.

As for all antiplatelet drugs, it cannot be entirely excluded at this stage of development that Revacept could potentially increase bleeding propensity. Especially the likelihood of bleeding problems might occur in combination with multiple anti-thrombotic or antiplatelet drugs.

The immunogenicity of Revacept is judged to be considerably low, as its components are naturally occurring in the human body and should hence be recognised as 'self'. As for all therapeutic proteins, there is residual risk for Revacept triggering an aberrant immune reaction. Potential allergic responses may produce mild symptoms such as skin rashes and flu-like symptoms but also severe and potentially life-threatening reactions such as anaphylactic shocks. In order to minimise the risk of acute allergic reactions, patients with a history of allergic responses to any component of the study drug (GPVI-Fc, mannitol, sucrose), acetylsalicylic acid or clopidogrel will be excluded from study participation.

Although the risk for production of anti-drug antibodies is low for single dose application, anti-Revacept autoantibodies could potentially cross-react with circulating platelets. For minimisation of this risk, patients with a known history of thrombocytopenia will not be allowed to participate in this study.

Taken together is Revacept a very novel, highly specific and remarkable antithrombotic strategy without affecting normal thrombocyte function. The development of Revacept was initiated in a long way of fundamental research by scientists of Ludwig-Maximilians-Universität (LMU) and Technical University (TU) Munich. Conducting this trial helps to shorten the time of the transfer of this promising, research-initiated approach into clinical use. The present randomized, double-blind, placebo-controlled, phase II trial will assess the efficacy and safety of Revacept in patients to provide guidance for a subsequent phase III study.
The hypothesis of this trial is that Revacept is able to reduce ischemic complications in patients with stable CAD undergoing elective PCI without compromising systemic haemostasis.

3. STUDY MEASURES (ENDPOINTS)

The main objective is to evaluate the efficacy and safety of treatment with 2 doses (80 and 160 mg) of Revacept versus placebo. Periprocedural antithrombotic therapy composed of clopidogrel, ASA and heparin (or bivalirudin) will be administered based on local practice and current guidelines. The treatment effect will be assessed using the following endpoints:

- Primary endpoint of the study

  A composite endpoint of death or myocardial injury (defined as increase in cardiac biomarker – high sensitivity cardiac troponin T of at least 5 times the upper limit of norm (ULN)) within 48 hours from randomisation.

- Secondary endpoints

- Peak high-sensitivity troponin T level within 48 hours from randomisation

  to be evaluated within 30 days after randomisation and will include:

- All-cause mortality
- Myocardial infarction
- PCI-related (type 4a) myocardial infarction
- Definite stent thrombosis
- Urgent coronary revascularization
- Stroke
- Bleeding complication class 2 or higher according to Bleeding Academic Research Consortium (BARC) criteria (safety endpoint)

4. ETHICAL CONSIDERATIONS

4.1. Good Clinical Practice

The investigation will be performed in accordance with the Declaration of Helsinki (2013), Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), in accordance with the ethical principles underlying European Directive 2001/20/EC and applicable local laws and regulations, in particular, the German GCP-Verordnung and Arzneimittelgesetz.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive approval/favourable opinion of the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (corresponding regulatory authority) and Independent Ethics Committee (IEC) prior to initiation of the study.

All potential serious breaches must be reported to Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety, physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this clinical trial will be qualified by education, training, and experience to perform their respective task(s). Systems with procedures that assure the quality of every aspect of the study will be implemented.

4.2. Independent Ethics Committee (IEC) and Regulatory Authority(ies)

It is the responsibility of the Sponsor to obtain approval of the Clinical Trial Protocol/ amendments from the IEC and Regulatory Authorities according to local regulatory requirements. The Sponsor should file all correspondence with the IEC and Regulatory Authorities.

The Sponsor is responsible for keeping the IEC and Regulatory Authorities informed of the progress of the study and of any subsequent modifications to the protocol as deemed appropriate. This should be performed at least once annually. The Sponsor must also keep the IEC and Regulatory Authorities informed of any serious adverse reactions according to local regulatory requirements. In addition, the patient informed consent (or other appropriate document) should allow for release of the patient records for investigation documentation purposes.

4.3. Patient information and consent

It is the responsibility of the Investigator to give each patient, prior to inclusion in the study, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. Written informed consent must be obtained at screening in accordance with good clinical practice and local legislation prior to enrolment and randomisation.

After the written informed consent form and any other written information has been read and explained to the patient, the patient will sign and personally date the informed consent form. By signing the consent form, the patient attests that the information in the consent form and any other written information was accurately explained and apparently understood, and that the patient freely gave the informed consent. In addition, the Investigator who obtains the consent must sign and date the consent form.

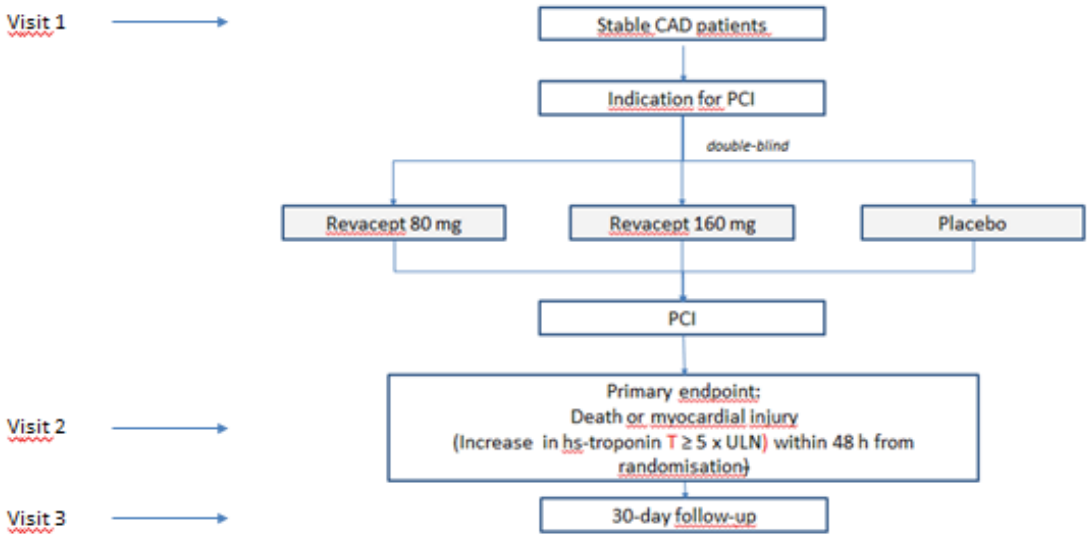
The patients must be informed of their right to withdraw from the investigation at any time. Signed consent forms must remain in the Investigator Site File and must be available for verification by study monitors or local authorities at any time.

The informed consent and any other information provided to subjects, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IEC approval/favourable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented. During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject and have to be signed by the subjects enrolled in the trial who are affected by the amendment.

5. INVESTIGATIONAL PLAN

5.1. Study Design and Duration

This is a multicenter, double-blind, dose-finding, placebo-controlled, 3-arm randomised phase II study. Eligible subjects will be randomised to one of three treatment groups, receive study treatment and undergo safety measures. The randomisation will be stratified by study centre. Follow ups are scheduled at 48 hours and 30 days after randomisation.



The study is conducted at a minimum of three study centres which will include a total number of 332 (placebo: n = 90; in each of the Revacept group: n = 121) patients.

The centres should have solid experience in clinical research and profound knowledge of GCP. Moreover, participating Investigators should have special interest in studying patients with coronary artery disease.

5.2. Study Population

It is imperative that subjects fully meet all eligibility criteria.

5.2.1. Inclusion Criteria

For entry into the study, the following criteria MUST be met:

1) Signed written informed consent

2) Target population

a) Men and women aged >18 years

b) Diagnosis: Clinically stable coronary artery disease

c) Angiographic evidence of coronary artery disease

d) Indication for PCI

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after receiving investigational product in such a manner that the risk of pregnancy is minimised.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g. vasectomy) are considered as adequate methods of contraception. Women who are using methods named above should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to randomisation.

5.2.2. *Exclusion Criteria*

Subjects must not be included for any of the following reasons:

1) Sex and reproductive Status:

- WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for up to 4 weeks after receiving investigational product.
- Women who are pregnant or breastfeeding or are planning pregnancy during course of trial
- Women with a positive pregnancy test on enrolment or prior to investigational product administration.

2) Medical history and concurrent disease

- Patients with elevated high sensitivity cardiac troponin T levels at screening
- Patients receiving antithrombotic therapy with Prasugrel or Ticagrelor within 7 days prior to randomisation
- History of hypersensitivity, contraindication or serious adverse reaction to any component of the study drug (GPVI-Fc, mannitol, sucrose), acetylsalicylic acid or clopidogrel
- History of bleeding diathesis or active bleeding within the last 30 days
- Recent intracerebral haemorrhage or trauma within the last 3 months
- Thrombocytopenia (platelet count <30000/mm^3) at screening

- Sustained hypertension (systolic BP >179mmHg or diastolic BP >109mmHg) at screening
- Renal failure (estimated glomerular filtration rate < 30 ml/min and/or dialysis)
- Severe systemic disease, such as known malignancies or other co-morbid conditions with life expectancy less than one year that may result in protocol non-compliance
- Unable to provide informed consent (e.g. severe dementia, or psychosis)
- Current severe liver dysfunction (transaminase level >5-fold the upper normal range limit)
- Patients with an indication for anticoagulant therapy
- Participation in any other clinical intervention trial (drug/device) within less than 30 days prior to screening
- Any other contraindication to perform PCI
- Any planned additional PCI or surgery within 30 days after randomisation
- Suspected poor capability to follow instructions and cooperate
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness (e.g. infectious disease)

5.2.3. Discontinuation of Subjects from Treatment or study participation

If a subject was withdrawn before completing the study, then the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

Subjects will be withdrawn from the study for the following reasons:

- withdrawal of consent by the subject for any reason at any time
- if continued study participation is not in the best interest of the subject, as judged by the Investigator (e.g. due to clinical adverse event (AE), laboratory abnormality or intercurrent illness)
- Termination of the study by regulatory authorities or ethics committee
- Subjects, who become prisoners, involuntarily incarcerated or compulsorily detained for treatment of either a psychiatric of physical (e.g. infectious disease) illness

Patients who discontinue study participation prior to visit 2 for any reason will be invited to skip to follow up visit 3.

5.2.4. Follow-up of Discontinued Subjects

If the reason for withdrawal is a serious Adverse Event (SAE), the Investigator will follow the case up to resolution and provide Sponsor with a final report of this SAE or justify why no final report will be provided.

5.3. Duration of trial

5.3.1. Trial Duration

The total duration of this study is planned until 332 patients are recruited.

Start date: 14 Nov 2017
Planned recruiting period: 29 months
Planned LPFV: Feb 2020
Planned LPLV: Mar 2020

5.3.2. Duration per patient

Trial duration per subject will be 30 days.

6. TREATMENT

6.1. Study Treatment

In this protocol, the investigational products are Revacept and placebo (phosphate buffered saline, 1% sucrose, 4% mannitol).

6.1.1. Non-investigational Product

Study plan does not include non-investigational medicinal product.
Besides IMP, all other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, are components of the standard of care for a given diagnosis.

6.1.2. Supply of study medication

Labelling and release of drug product is conducted at advanceCOR GmbH, Martinsried, Germany. Investigational product will be sent to individual study sites after site initiation.
Additional IMP supplies will be sent to individual study sites upon request.

6.1.3. Identification, packaging and labelling of study medication

IMP will be supplied to each study centre in kit boxes. Each kit box contains four IMP vials that make up one dose of trial medication for one patient. Each of the four vials contains 16.7 ml of clear solution of either:

- Placebo (phosphate buffered saline (PBS), 1% sucrose, 4% mannitol) or
- 40 mg Revacept (2.4 mg/ml in PBS, 4% mannitol, 1% sucrose)

6.1.4. Handling and dispensing of study medication

advanceCOR will provide the investigational medicinal product to individual study sites. The Investigator or member of his team if this task is delegated will sign the Drug Receipt Form confirming receipt of clinical supplies for the study and provide assurance that the investigational product will be handled and stored properly. It is the responsibility of the Principal Investigator to ensure that investigational product is only distributed to trial participants. The investigational product must be dispensed by authorised personnel only. The Principal Investigator will ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by advanceCOR. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact advanceCOR immediately.

6.1.5. Drug Accountability and Return and Destruction of Investigational Product

At the Study Centre

Used /partially used vials	Disposal at site according to local policy after drug accountability has been performed by the monitor and the confirmation for destruction has been given by the monitor
Drugs left unused / expired	Return to advanceCOR GmbH, preferably in the original package, Return must be documented.

6.1.6. *Treatment Administration*

Revacept/placebo will be administered once per patient by intravenous infusion as described in the handling instructions of the study medication. One patient dose is prepared by combining 4 IMP vials of a single kit box. All vials of a kit box should be equilibrated to room temperature before combining them in two 50 ml perfusor syringes. An in-line filter rated for perfusor syringes use must be inserted in the perfusor infusion line.

6.2. Randomisation

The randomly distribution of the different treatment groups consisting of Placebo, Revacept 80 mg and 160 mg will be done by an online randomisation program available at:

https://www.randomizer.at/random/web/login.php

Randomisation will be performed in a double-blinded manner with the use of a central computerized system, embedded in the eCRF. The randomisation will be stratified by study centre.

6.2.1. *Blinding/Unblinding*

Emergency unblinding is performed using the web-based online randomisation tool available at https://www.randomizer.at/random/web/login.php. The Investigator should ensure that the code is broken only in accordance with the protocol. For unblinding, the Investigator should note the date, time and reason for unblinding in the patient notes and CRF and promptly inform advanceCor, the Sponsor and the Coordinating Investigator of any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s). In addition sealed emergency randomisation envelopes will be kept at study centers and the Sponsor (Phone: +49 (0)89 1218 2785) as a back-up solution if the online randomisation tool is not available.

Reasons for premature unblinding may be any of the following situations:

- In case of an emergency situation, if it is necessary for the patient´s safety, i.e. if the further treatment depends on the knowledge of the study medication
- In the event of the death of a patient, if a causal relationship between the treatment with the study medication and the death is suspected.
- In the event of SAEs/SUSARs if a causal relationship between the treatment with the study medication and the event is suspected

6.3. Supportive Care

The accompanying medication will encompass the entire spectrum medication for treatment of coronary artery disease in accordance with the corresponding guidelines. The investigation plan will in no way present restrictions in this sense, see section 5.2.2 for prohibited treatments. Most importantly, this clinical trial will not delay or hinder percutaneous coronary intervention. Any required concomitant medication and any changes of concomitant medication in accordance with clinical needs will be documented in the patients´ medical records and in the CRF. Furthermore all other concurrent diseases (not part of the exclusion criteria) will be treated according to the corresponding guidelines.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Procedures by visit

Informed consent must be obtained prior to any study procedure that would not have been performed as part of normal subject care. However, data obtained as part of the normal subject care can be used for Visit 1/ Screening and Visit 2. Additional follow-up visit(s) will be required every 4 weeks until all study related toxicities resolve to baseline, stabilise or are deemed irreversible, whichever is longer. Any additional medical testing and procedures, whether more frequent or in addition to those described, should be performed as medically indicated.

7.1.1. *Visit 1 / Screening – Administration of Study Medication*

The following procedures are performed at screening:

The screening data are considered valid only if collected within 2 days prior to randomisation.

- Informed consent must be obtained prior to conducting any procedure that would not have been performed as part of normal subject care.
- Assessment of inclusion and exclusion criteria.
- Date of birth, gender, race, general medical and surgical history (including concomitant medication at screening) will be recorded.
- Physical examination including measurement of body weight and height, pulse rate and blood pressure and assessment of heart, lung and abdomen will be performed.
- Electrocardiogram (ECG)
- High sensitivity cardiac troponin T
- Clinical biochemistry, clinical haematology, coagulation, endogenous GPVI levels, platelet related inflammatory mediators and platelet released microRNA
- At predefined study centres: Platelet aggregation tests (response to collagen and ADP)
- Pregnancy tests are to be performed for all eligible women of childbearing potential (WOCBP).
- Angiography: Evidence of coronary artery disease

Once all examination results are available and indicate that the patient is eligible for the study which means that the patient meets all inclusion and none of the exclusion criteria, the study medication will be administered according to randomisation sequentially. Successfully screened subjects may be re-screened if necessary.

- Administration of study medication will be performed by intravenous infusion. Patients are to be kept under medical supervision.
- Assessment of adverse events
- Assessment of bleeding according to BARC criteria

7.1.2. *Visit 2 / 48h after randomisation +/- 12 h*

- Physical examination including measurement of body weight, pulse rate and blood pressure and assessment of heart, lung and abdomen will be performed.
- Review of concomitant medication
- Assessment of adverse events
- Assessment of bleeding according to BARC criteria
- Electrocardiogram (ECG)
- High sensitivity cardiac troponin T

- Clinical biochemistry, clinical haematology, coagulation, endogenous GPVI levels, platelet related inflammatory mediators and platelet released microRNA
- At predefined study centres: Platelet aggregation tests (response to collagen and ADP)

7.1.3. Visit 3 / Follow Up 30 days after randomisation +/- 7 days

- Review of concomitant medication
- Assessment of adverse events
- Assessment of bleeding according to BARC criteria

A scheme summarising all visits, interventions and assessments planned is shown below:

Procedure / Visit	*Visit 1 / Screening & Treatment*	*Visit 2 / 48h +/-12h after randomisation*	*Visit 3 / Follow Up – 30 days +/-7 days after randomisation*
	1	2	3
Written informed consent	x		
Assessment of in-/exclusion criteria	x		
Demographic data, review of medical and surgical history	x		
Review of concomitant medication	x	x	x
Physical examination (vital signs etc.)	x	x	
Electrocardiogram	x	x	
High sensitivity cardiac troponin T	x	x	
Soluble GPVI or GPVI expression, platelet related inflammatory mediators and platelet released microRNA	x	x	
Biochemistry	x	x	
Haematology	x	x	
Coagulation	x	x	
Platelet aggregation tests at predefined study centers	x	x	
Pregnancy test	x		
Angiography	x		
Administration of study medication and PCI	x		
Assessment of adverse events	x	x	x
Assessment of BARC bleeding	x	x	x

7.2. Details of Study Procedures

7.2.1. Review of anamnesis

General medical and surgical history (including concomitant medication) will be recorded at screening.

7.2.2. Physical examination

Body height will be documented according to patient´s declaration. Body weight will be measured at visit 1. Heart rate, blood pressure and body temperature will be recorded at study visit 1 and 2. The heart rate will be taken by electrocardiogram. Blood pressure will be measured once on both arms while the subject is seated, for at least 5 minutes before measurement. Furthermore, physical examination of heart, lung and abdomen will be performed and any signs of peripheral oedema or ascites will be documented.

7.2.3. 12 lead-Electrocardiogram (ECG)

- Type of rhythm
- Heart Rate
- PQ interval
- QTc interval
- Assessment of ST-segment deviation (elevation or depression)
- Q waves
- Left bundle branch block

7.2.4. Percutaneous coronary intervention

- Assessment of lesion and flow characteristics
- Treatment
- Assessment of final PCI result

7.2.5. Bleeding assessment according to BARC criteria

BARC Criteria (Mehran et al, 2011): For detailed description please refer to Appendix A.

7.2.6. Assessment of adverse events

Adverse events will be closely monitored including any unexpected effects on myocardial injury and bleeding events.

7.2.7. Myocardial injury

It is assessed by high sensitivity cardiac troponin T level measured at 48 hours

7.2.8. Clinical endpoints

Clinical endpoints will be assessed at 30 days after randomisation. The following measures will be recorded:

- All-cause mortality
- Myocardial infarction
- PCI-related (type 4) myocardial infarction

- Definite stent thrombosis
- Urgent coronary revascularization
- Stroke

7.2.9. Clinical Chemistry: Biochemistry, Haematology, Coagulation (in-house)

Biochemistry

- ALAT/SGPT, alkaline phosphatase, ASAT/SGOT, blood urea or urea nitrogen, cardiac troponin T, CK, CK-MB (not mandatory if CK is within the normal range), γ-GT, creatinine, estimated GFR, lactate dehydrogenase, glucose, sodium, potassium, total bilirubin, total cholesterol (only at screening), triglycerides (only at screening), uric acid and C-reactive protein (CRP) will be determined.

Haematology

- Haemoglobin, platelet count, white blood cell count (WBC) and red blood cell count (RBC), mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, hematocrit. Neutrophils, lymphocytes, eosinophils, basophils and monocytes.

Coagulation

- Activated partial thromboplastin time (aPTT), prothrombin time (PT), International normalisation ratio (INR)

7.2.10. Soluble GPVI / GPVI expression on platelets, platelet relatedinflammatory mediators, platelet released microRNA

Soluble GPVI or GPVI expression on platelets will be characterised as patient-specific factors that may predict Revacept treatment success. Analyses will also focus on platelet related inflammatory mediators including chemokines and cytokines such as Interleukin-8, MCP-1, RANTES, CXLC5. In addition, platelet microRNA in plasma will be analysed to better characterize platelet function. All analyses will be performed at advanceCOR laboratory.

7.2.11. Pregnancy test (in-house)

For women of child-bearing potential (WOCBP) a blood or urine pregnancy test (minimum sensitivity 25 IU/L) will be performed at screening (visit 1).

7.2.12. Platelet aggregation tests

Platelet aggregation tests will be performed at predefined study centres.

Platelet aggregation tests

In vitro platelet aggregation tests will be performed after stimulation with collagen and ADP. Details on sample processing, test performance and logistics will be provided to the individual centres prior to trial initiation.

7.3. Safety Assessments

The safety variables are AE, SAE, and in addition data from physical examination, routine laboratory results, body temperature, ECG, blood pressure and heart rate. Study drug toxicities will be assessed continuously. Adverse events will be classified as outlined in section 8 below.

8. ADVERSE EVENTS

8.1. Definitions

An **adverse event (AE)** is defined as any untoward medical occurrence in a patient or clinical trial subject administered an medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory 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, i.e. a disorder present before randomisation in the clinical trial should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during study participation.

Adverse drug reactions (ADRs) are all untoward and unintended responses to an investigational medicinal product related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between event and IMP. This means that there are facts (evidence) or arguments to suggest causal relationship.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalisation or causes prolongation of existing hospitalisation* (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect, or
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardise the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation.)

All pregnancies, regardless of outcome, must be reported to the Sponsor on a Pregnancy Report Form, not an SAE form.

* The following hospitalisations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered “important medical event” or “life threatening” event)

- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical admission for purpose other than remedying ill health state and was planned prior to signing informed consent. Appropriate documentation is required in these cases
- admission for social reasons encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an adverse reaction, the nature or severity of which is not consistent with the Investigator´s Brochure.

The sponsor will assess each SAE concerning seriousness, causality and expectedness to ensure ongoing safety evaluation and reporting obligations.

In addition a risk-benefit evaluation will be performed by the sponsor describing whether the SAE report implies a safety issue that
- might alter the risk-benefit assessment
- might be sufficient to consider changes in the conduct of the study.

8.2. Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following guidelines and definitions should be used by the Investigator for the description of an AE when reporting information:

Nature of the AE :		Preferably an overall diagnosis or syndrome, rather than individual symptoms or signs should be reported. The Investigator must report adverse events using standard medical terminology. Any discrepancies between the subject's own words on his/her own records (e.g. diary card) and the corresponding medical terminology should be clarified in the source documentation.
Date of onset:		Date the AE started.
Intensity:		
	Mild	The subject is aware of the sign or symptom *(syndrome)*, but it does not interfere with his/her usual activities and/or it is of no clinical consequence.
	Moderate	The AE interferes with the usual activities of the subject or it is of some clinical consequence.
	Severe	The subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence.

Actions taken :		All actions taken are to be noted
	None	No action was taken for this AE
	Concomitant medication	Drug treatment: the subject took a concomitant medication (either prescription or non-prescription) specifically for this AE OR existing concomitant medication dosage was modified as a result of this AE.
	Therapeutic or diagnostic procedure	Subject used other therapeutic measures (e.g. ice, heating pad, brace, cast, etc.) or subject underwent a diagnostic procedure (e.g., additional lab test, x-ray, etc.) for this AE.
Date of resolution:		Date the AE resolved. If the AE consists of several signs and symptoms (syndrome), the sign or symptom with the longest duration determines the duration of the AE. If the AE is marked "ongoing", the outcome date should be blank.
Outcome:		
	Recovered/ resolved	The AE is no longer present at any intensity - completely abated.
	Recovering/ resolving	The AE not yet resolved, but symptoms have improved.
	Resolved with sequelae	The AE is resolved but residual effects are still present.
	Not recovered/ not resolved	The AE is still ongoing at the last contact with the subject.
	Fatal	This AE caused or directly contributed to subject's death.
	Unknown	The outcome of the AE is not known.

Relationship to investigational product (causality):

The following should be considered for evaluation of causality:

- a temporal relationship
- a pharmacologically or biologically plausible event
- positive dechallenge after stopping respectively rechallenge after restarting of IMP
- presence of confounding factors, such as concomitant medication, concurrent illness or relevant medical history

Not related	There is not a reasonable possibility that the AE is related to the IMP. Alternative etiology, diagnosis or explanation for the event should be provided.
Related	There is a reasonable possibility that the AE is related to the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

8.3. Collection and Reporting

The trial participant will be given the opportunity to report AEs spontaneously to the Investigator. A general prompt will also be given to detect AEs at each study visit after treatment has been administered, e.g., "Did you notice anything unusual about your health (since your last visit)?" (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded by the Investigator, rather than its individual symptoms. The following information should be captured for all AEs: onset, stop date (duration), intensity, seriousness, relationship to investigational medicinal product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the concomitant medication page of the CRF. The Principal Investigator shall supply the Sponsor, all Ethics Committees involved, and Regulatory Authority with any additional requested information, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

8.3.1. *Serious Adverse Events*

Following the subject's randomisation all SAEs must be collected by the Investigator, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur until visit 3. The Investigator should notify Sponsor of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page of the CRF.A SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported by the Investigator to the Sponsor immediately (latest within 24 hours) after becoming aware of the event by entering the event in the respective SAE section of the eCRF. In some instances when the eCRF is not available the SAE should be reported by confirmed facsimile transmission (fax). If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same Investigator term(s) initially reported.) If the Investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (e.g. withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page of the CRF.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the Sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed up until resolution or stabilisation.
SAE reporting contact details are provided to each site through study specific instructions.

8.3.2. Handling of Expedited Safety Reports

Sponsor will notify Principal Investigators and advanceCOR of all suspected SAEs that are related to the investigational product and unexpected (i.e. not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the Sponsor as an ESR include: increased frequency of a clinically significant expected SAE, unexpected outcome of expected SAEs, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g. animal) study, or Sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from Sponsor, the Principal Investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IEC for the study, the Sponsor will submit the ESR to the appropriate Ethics Committee. The Sponsor and Ethics Committee will determine if the informed consent requires revision. The Sponsor should also comply with the Ethics Committee procedures for reporting any other safety information.

8.3.3. Non-serious Adverse Events

Following the subject's randomisation all identified non-serious AEs must be recorded and described on the appropriate non-serious AE page of the CRF.

If an ongoing non-serious AE worsens in its intensity or its relationship to the investigational product changes, a new non-serious AE entry for the event should be completed. Non-serious AEs should be followed-up until resolution or stabilisation, or reported as SAEs if they become

serious (see Section 8.3.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with non-serious AEs at study completion should receive post-treatment follow-up as appropriate. If no follow-up report is being provided, the Investigator must provide a justification.

8.4. Laboratory Test Abnormalities

All laboratory test abnormalities captured as part of the study should be recorded on the appropriate pages of the CRF. In addition, the following laboratory abnormalities should also be captured on the non-serious AE CRF page or SAE CRF page as appropriate:

- Any laboratory test result that is judged clinically significant by the Investigator or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the investigational product discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting Investigator (e.g. anaemia versus low haemoglobin value).

8.5. Overdose

An overdose is defined as the accidental or intentional administration of any dose of an investigational medicinal product. All occurrences of overdose must be reported as an AE/SAE.

8.6. Pregnancy

WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimised.

8.6.1. Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test within 72 hours prior to receiving the investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive the investigational product and must not continue in the study.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

8.6.2. Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, the Investigator must immediately notify Sponsor of this event and record the pregnancy on the Pregnancy Report Form (not an SAE form). Initial information on a pregnancy must be reported immediately to Sponsor and the outcome information provided once the outcome is

known. Completed Pregnancy Report Forms must be forwarded to Sponsor according to SAE reporting procedures described in Section 8.3.1.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported.

8.7. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate non-serious AE page or SAE reporting section of the eCRF.

9. STATISTICAL CONSIDERATIONS

9.1. Endpoint and Exploratory Analysis

Endpoint analysis will be performed when 332 patients have completed visit 3. Endpoint and exploratory analysis includes all data generated from visits 1 to 3.

9.2. Data Management

9.2.1. Data Handling and Quality Control

Data management and data quality assurance will be performed in compliance with international guidelines (e.g. ICH-GCP), SOPs and working instructions effective at that moment in time.

All study data will be entered remotely by authorized study personnel at the participating sites into the validated electronic data capture system (EDS) hosted by the Sponsor's contractor. Via standard browsers the users will access an electronic case report form (eCRF) in order to document patient data in the trial data base. According to the study's data validation plan (DVP) automatic edit checks will be implemented into the eCRF in order to detect data discrepancies. Both automated and manual checks are essential to guarantee data quality. The sites take responsibility to clarify, confirm or change questionable data accordingly. All query answers provided by the sites are reviewed closely by the data management department in order to decide whether a query may be considered closed or not and if requerying is required.

The EDS system contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the Investigator's site and at the Sponsor's. Data entries made in the EDC screens are supported by source documents maintained for all subjects enrolled in this study.

It is the expectation of the Sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for data points collected and the monitor will work with the site to complete this.

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- demographic information (subject number; year of birth / age; sex; if applicable race / ethnicity)
- date of informed consent
- reason for premature discontinuation
- date of last visit

These data will be transferred to the respective database.

All personnel with access to the EDS system are supported by a user helpdesk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

Prior to documentation of the first patient record (FPFV) in the trial data base a finalized and fully approved data management plan (DMP) has to be in place. This plan will define all study specific data management processes in detail and has to be updated and newly approved once changes in data management processes during the conduct of the study should take effect.

All other details are described in the data management plan.

9.2.2. Data Coding

For data coding (e.g. AEs), internationally recognized and accepted dictionaries (e.g. MedDRA Version 13.0 or higher) will be used.

9.2.3. Database Lock

Both soft and hard lock of the study data base will only take place in accordance with the Sponsor's SOP for data base lock to ensure that:

- all study data have been entered accordingly
- decisions have been agreed upon on how individual protocol violations are to be dealt with
- written authorisation from the Sponsor has been granted

9.3. Statistical Procedures

9.3.1. Sample Size Estimation

Two ordered hypotheses will be tested. The first hypothesis to test is that whether there is a significant difference in the primary endpoint among the 3 study groups in favor of Revacept treatment. Sample size calculation was based on the following assumptions: incidence of the primary endpoint of 25% in the placebo group (as shown by a recent analysis of 2000 patients meeting study criteria from the database of the Deutsches Herzzentrum München) and 8% and 17% in the higher and lower Revacept doses groups, respectively (corresponding to an overall 50% relative risk reduction in the combined Revacept doses groups vs. placebo), 2-sided alpha-level of 0.05 and power of 80%. These assumptions led to a total sample size of 270 patients, 90 patients in each of the 3 study groups (calculated with nQuery). Because it is a short-term study encompassing only 48 hours from the index procedure, no drop-outs are expected.

If there is a statistically significant difference between the three study groups, a comparison between the 2 Revacept doses groups will follow in a second step. One way to select the better of the two Revacept groups is to select the dose with the larger response rate (Simon et al. 1985). The other way is to increase the type I error rate at α=20% (Rubinstein et al. 2005). We will apply the latter approach. Concerning the second hypothesis, the comparison of the study doses, based on the given sample size in order to detect a difference between 8% and 17% with a power of 80% using type I error rate of 20%, 121 patients per group (in total 242 patients) are needed. This means that we have to enroll a total of 332 patients in this study (90 patients in

placebo group and 121 patients in each of the Revacept doses groups). In the case that the study meets the first but not the second hypothesis in statistical terms, an overall evaluation of both efficacy and safety findings will be performed. In General, comparability of the results will be in support of the lower dose to be used in subsequent trials involving this category of patients.

9.3.2. Statistical Analysis

The comparison of characteristics between the 3 groups will be performed by the Chi-square test or Fisher's exact test as appropriate. The continuous data will be compared by the use of the Kruskal-Wallis rank-sum test. Analysis of the primary and secondary efficacy endpoints will be performed according to the intention to treat principle, analysis of the safety endpoints according to modified intention to treat principle. The treatment effect across the 3 groups will be assessed by the test for trend using the logistic regression by assigning 0 to the placebo group, 1 to the lower-dose Revacept group and 2 to the higher-dose Revacept group. The logistic model will account for stratification according to the participating centers. The use of a logistic model that accounts for stratification factors is in accordance with "Statistical Principles for Clinical Trials" ICH Topic E9. If there is a significant difference between the three groups the two Revacept groups will be compared by using the chi-square test.

9.3.3. Definition of Populations

Before study unblinding or data review, possible protocol violations will be classified as "major", "minor", or "none". Subjects will be allocated to the individual data sets with regard to the classification of possible protocol violations. The final data sets shall be described in detail in the Blind Review Report.

ITT Population

For efficacy, all subjects who have been randomised will be included in the intention-to-treat analysis.

Modified ITT Population (Safety population)

Modified ITT population includes all patients belonging to the ITT population who have received any study medication. This will be the population included in the safety analysis.

Per-Protocol (PP) Population

The PP population includes all subjects who are eligible for ITT evaluation and who, in addition, do not show major protocol deviations. The PP population only includes subjects for whom eligibility could be confirmed.

9.3.4. Missing Values

Rules on how missing values of efficacy variables will be replaced are to be described in the Statistical Analysis Plan. Since study medication is administered as one-time infusion immediately after randomisation in the catheterization laboratory, compliance to study medication is expected to be close to 100%.

9.3.5. *Software*

Data analysis will be performed in a validated working environment in compliance with the requirements of the ICH-Guidelines E9 [1998]. The software to be used for data evaluation will be described in the statistical analysis plan.

9.3.6. *Safety Analysis*

Physical examinations and vital signs

Findings of physical examinations and changes in vital signs (blood pressure and heart rate) from baseline will be presented with descriptive statistics.

Adverse events

Adverse events (AEs) will be categorised by primary system organ class (SOC) and MedDRA preferred term as coded using the MedDRA dictionary. The number, intensity, relation to study medication and action taken will be described by frequency tables.

Laboratory variables

Laboratory variables will be presented as:

- Tables with raw values ("data as available") and descriptive statistics with markings of values outside reference range and
- Tables with changes from baseline and with descriptive statistics.

9.4. *Final Statistical Analysis Plan*

The statistical analysis plan will be included in the Blind Review Report and finalised by the statistician before the blind will be broken and decoding takes place.

9.5. *Quality Control*

Statistical analysis will be performed according to the statisticians SOPs, the statistical analysis plan, the clinical study protocol and all its amendments. All evaluation steps will be completely documented and the software to be used is validated. In-process controls will be performed and documented.

10. ADMINISTRATIVE SECTION

10.1. Investigational Site Training

Sponsor will provide investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, investigational product, study documentation, informed consent and enrolment of WOCBP.

10.2. Allocation of Responsibilities

All participating Principal Investigators and their deputies are to be approved by an Independent Ethics Committee before performing any study assessments.

The Principal Investigator of a particular study centre is responsible for the implementation of the protocol but can delegate tasks to the research team. He/she remains responsible for coordinating and informing his/her staff about the protocol and the possible changes made to it.

The Principal Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties ("Medical Staff List" document with name, function, signature, initials, dates of participation in the trial conduct and type of delegated tasks). This list should be kept up to date.

10.3. Curriculum Vitae (CV)

The Investigator should supply his/her updated CV, dated and signed, together with a list of his/her collaborators responsible for the practical conduct of the trial. These collaborators should also provide a recent version of their CVs, dated and signed.

10.4. Subject Insurance

Sponsor declares that insurance will be subscribed, for the total duration of the trial, covering the subjects, in respect of the risks involved in this trial carried out according to this protocol. In case of injury or disability deriving from participation in the study, the subject is requested to inform without delay the insurance company and the treating physician responsible for the trial. In addition the Sponsor contracted a travel accident insurance for patients at the same insurance company.

HDI-Gerling Industrie Versicherung AG
Niederlassung München
Ganghoferstr. 37 - 39
80339 München

10.5. Study Participation Card and GP Information Letter

Subjects will be given a study participation card containing emergency contact details and will be asked to keep this with them at all times until the last visit of the study. Patients will be offered written notification of their GP.

10.6. Pharmaceutical Manufacturer of the IMP

The pharmaceutical manufacturer of the IMP Revacept is:

advanceCOR GmbH
Fraunhoferstraße 9a
D-82152 Martinsried
Germany

and therefore responsible according to AMG ("Gesetz über den Verkehr mit Arzneimitteln") for:

- Manufacturing (§§ 13,19)
- Release (§§ 9, 19)
- Labelling (§ 10)

of IMP Revacept for this clinical trial.

10.7. Compliance

10.7.1. Compliance with the Protocol and Protocol Revisions

The Investigator should conduct the trial in compliance with the protocol agreed to by Sponsor, the Regulatory Authority(ies) and for which an approval by the IEC was given. The investigator and Sponsor should sign the protocol to confirm agreement.

A protocol deviation should only occur in an emergency that requires such a procedure, for example an Adverse Event. The Investigator must contact the monitor or Sponsor by telephone as soon as possible. An explanatory note in the eCRF will describe the deviation from the protocol and state the reason for it.

Normally, all other deviations should be discussed in advance through the trial monitor and agreed with Sponsor. Every deviation must be documented in the eCRF.
Any significant protocol deviation will be documented and explained by the Investigator or the person designated by the Investigator and will be included in the clinical trial report.

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by Sponsor. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the eCRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IEC approval/favourable opinion, as soon as possible the deviation or change will be submitted to:

- Sponsor
- IEC for review and approval/favourable opinion

Documentation of approval signed by the chairperson or designee of the IEC(s) must be sent to Sponsor. If an amendment substantially alters the study design or increases the potential risk to the subject:
(1) the consent form must be revised and submitted to the IEC(s) for review and approval/favourable opinion;
(2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and
(3) the new form must be used to obtain consent from new subjects prior to enrolment.

10.7.2. Monitoring

The arrangement for proper monitoring of the trial is the responsibility of the Sponsor. The monitor (the individual responsible for monitoring) will advise the Investigator regarding the practical conduct of the trial and assist him/her in working according to the protocol, ICH/GCP, and the regulatory requirements.

The Principal Investigator will allow the monitor to periodically monitor at mutually convenient times during and after the trial has been completed, all eCRFs and the corresponding source documents. Therefore, the monitor will have direct access to these records. The extent and frequency of monitoring and percentage of source data verification performed will be defined in the Monitoring Plan. Depending on recruitment rate and data quality of individual study sites, the extent of monitoring will be increased or adapted as required. The monitoring visits provide the monitor with the opportunity to evaluate the progress of the trial, to verify the accuracy and completeness of CRFs, to ensure that all protocol requirements, applicable local authority regulations and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the trial records.

The Principal Investigator will also allow Sponsor or its representatives to periodically co-monitor at mutually convenient times during and after the trial, all eCRFs and the corresponding source documents. Therefore, Sponsor or its representatives will have direct access to these records.

10.7.3. Steering Committee

The steering committee is responsible for overseeing the good execution and administrative progress of the protocol; will meet regularly to monitor patient accrual, non-compliance with protocol at individual centres, to act upon recommendations of DSMB, and to determine policy regarding individual publications arising from data generated from the performance of the study.

10.7.4. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be responsible for assessing the progress, safety data and critical efficacy endpoints of the trial. The main task of the DSMB is to monitor the safety of the participants of the clinical trial. Therefore the DSMB will be provided with the AEs and SAEs occurred during the conduct of the study. Based on its review the DSMB provides the Sponsor with recommendations regarding study modification, continuation or termination. All final decisions, however, regarding study termination or modification rest with the Steering Committee.

The following events will be reported to the DSMB after adjudication by the event adjudication committee: death of any cause, cardiac death, MI, definite stent thrombosis, urgent coronary revascularization, stroke and bleeding class 2 or higher.

The Sponsor decides on the selection of the DSMB members. The DSMB meetings will take place at least once per year. Detailed procedures will be described in the DSMB charter.

10.7.5. Event Adjudication Committee

The Event Adjudication Committee (EAC) will adjudicate suspected endpoints in order to provide a standardised, systematic, independent and unbiased assessment. The members will review the events reported by the Investigators as endpoints to determine whether they meet the specified criteria of endpoint definition. During event adjudication members of the committee are blinded to the randomized treatment received by the patient. More details are outlined in the EAC charter.

10.8. Direct Access to Source Data/Documents

The Principal Investigator(s)/institution(s) will permit trial-related monitoring, audits by or on behalf of Sponsor, IEC review, and regulatory inspection(s), providing direct access to source data/documents. Sponsor may also perform for-cause monitoring and/or audits in case of emergencies upon short notice.

Source documents are original records in which raw data are first recorded. These may be: hospital/clinic/General Practitioner (GP) records, charts, diaries, x-rays, laboratory results, ECG, and other printouts, pharmacy records, care records, completed psychometric scales, daily record cards, quality of life questionnaires, etc.

All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (e.g. ink, typing, printing, optical disc).

Hospital/clinic/medical files that are computer generated and stored on magnetic support media must be printed. The Investigator will sign and date the print-out. The Investigator will authorise the monitor to compare the content of the print-out and the data stored in the computer to ensure all data are consistent.

10.9. Audit and Inspection

The Principal Investigator will permit trial-related audits by auditors mandated by Sponsor and inspections by domestic or foreign regulatory authorities, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with the planned arrangements, ICH/GCP, and applicable regulatory requirements. The Investigator will provide direct access to all trial documents, source records, and source data. If a regulatory inspection is announced, the Principal Investigator will immediately inform Sponsor.

Representatives of Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

Sponsor will ensure that appropriate training relevant to the study is given to the medical, nursing, and other staff involved in each centre.

In addition, the study may be evaluated by auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities.

The Principal Investigator must notify Sponsor promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Sponsor.

10.10. Termination of the Trial

Upon completion of the trial, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- return of all trial data to Sponsor or its representative,
- data clarification and/or resolution,
- accountability, reconciliation, and arrangements for used and unused trial drugs,
- review of site trial records for completeness,
- discussion/ reminder on archiving responsibilities.

In addition, Sponsor reserves the right to temporarily suspend or prematurely discontinue this trial either at a single site or at all sites at any time for reasons including safety or ethical issues, severe non-compliance, recurrent non-compliance, or unsatisfactory enrolment with respect to quality or quantity.

If the study is prematurely terminated or suspended, Sponsor will promptly inform the Principal Investigators and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by Sponsor

10.11. Archiving and Data Retention

The Principal Investigator will maintain adequate records for the trial including medical records, laboratory reports, informed consent documents, drug disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All records are to be retained by the Principal Investigator for a minimum of 15 years, e.g. according to the applicable regulations and guidelines. He/she will contact Sponsor for authorisation prior to the destruction of any trial records or in the event of accidental loss or destruction of any trial records.
The Principal Investigator must retain investigational product disposition records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor, whichever is longer. The Principal Investigator must contact Sponsor prior to destroying any records associated with the study.

Sponsor will notify the Principal Investigator when the study records are no longer needed. If the Principal Investigator withdraws from the study (e.g. relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator). Notice of such transfer will be given in writing to Sponsor.

10.12. Publications

10.12.1. Statistical Trial Report

Data Management will prepare a statistical trial report according to the relevant ICH guidelines, on the basis of which the Sponsor will issue a final clinical trial report. The report will include a thorough description of the clinical and laboratory methods, a discussion of the results and a list of all measurements.
This report may be included in submissions to government drug regulatory authorities world-wide, or used for whatever reason considered appropriate by Sponsor. No use should be made of the report before approval by Sponsor.

The Coordinating Investigator will sign the report for approval.

10.12.2. Publication and Presentation Policy

The information generated by this trial is the property of the Sponsor. It is agreed that the results of the trial will not be submitted for presentation, abstract, poster exhibition or publication until Sponsor has reviewed and commented on such a presentation or publication manuscript. Sponsor does not hold overall right to veto publications and presentations. The Sponsor of the study is committed to the unrestricted and widespread dissemination of the results of the study. At the completion the study, an abstract reporting the primary results will be prepared by the Steering Committee and presented at an annual scientific cardiology meeting. A manuscript will similarly be prepared for publication.
The publication of the principal results from any single-center experience within the trial is not allowed before both the preparation and publication of the primary results.
Following analysis and presentation of the primary endpoint results, active participation of all committee members, Investigators from high enrolling sites, and core laboratory personnel will be solicited for data analysis, abstract and manuscript preparation. Submission of all abstracts

and publications regarding the primary and secondary endpoints from the study requires approval by the Steering Committee.

10.13. Investigator Site File

The content of the Investigator Site File is structured in a manner that aids in the filing, retrieval, and/or auditing of study-related documents. All documents will be filed according to standard file categories that identify specific aspects of the trial.

The contents and format of the Investigator Site File must conform to Annex 8 of the ICH-GCP guideline.

The Investigator Site Files will be prepared by and provided to the study sites by Sponsor.

10.14. Data Handling and Record Keeping

Data Management will be responsible for data processing under the supervision of Sponsor.

eCRF data will be entered in an electronic database using a clinical data management system. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. An electronic audit trail system will be used to track all data changes in the database. Regular back-ups of the electronic data will be carried out.

In case of screening failure, all data will be collected until the reason for screening failure becomes evident. The reason for screening failure (i. e. randomisation/treatment allocation status) will be entered into the clinical database and should therefore be monitored and retrieved from the site.

11. CORE LABORATORIES

All analyses for soluble GPVI or GPVI expression on platelets, platelet related inflammatory mediators and platelet released microRNA will be performed at advanceCOR core laboratory. Measurements will be done by personal blinded to treatment allocation and according to SOPs based quality management system.

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APPENDIX A (ENDPOINT DEFINITIONS)

DEATH (CUTLIP ETA L. CIRCULATION 2007):

Classifications of death:

Cardiac death:

Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Vascular death:

Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Non-cardiovascular death:

Any death not covered by the above definitions, such as
death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g. cancer, infection) is classified as cardiac.

BLEEDING

Bleeding Academic Research Consortium Criteria (Mehran et al Circulation 2011):

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: Overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3:

Type 3a: Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)
Any transfusion with overt bleeding

Type 3b: Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision

Type 4: CABG-related bleeding:
- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling Bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48h-period**
- Chest tube output ≥2L within 24h-period

Type 5: Fatal bleeding

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.
If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event.
If a bleeding event occurs with a clear temporal relationship to CABG (i.e. within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
** Cell saver products are not counted.

STENT THROMBOSIS (MAURI ET AL. N ENGL J MED. 2007):

According to Academic Research Consortium (ARC):

Definite stent thrombosis:
Presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion

Probable stent thrombosis:
Unexplained death within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.

Possible stent thrombosis:
All unexplained death occurring at least 30 days after the procedure.

Acute stent thrombosis:* Occuring within 24 hours following the index PCI
Subacute stent thrombosis:* 24 hours to 30 days following the index PCI
Late stent thrombosis: 31 to 360 days following the index PCI
Very late stent thrombosis: after 360 days following the index PCI

**Early stent thrombosis* includes patients with acute and subacute stent thrombosis (0-30 days following the index PCI).

STROKE (Hicks et al. Circulation 2018):

Stroke is defined as an acute episode of focal or global neurological dysfunction of at least 24 hours caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
Diagnosis of stroke should be confirmed by cCT or MRI or pathology.

Classification:
Hemorrhagic stroke: Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Ischemic stroke: Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Undetermined stroke: Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Modified Rankin Scale - Stroke severity assessment scale

Scale 0
No symptoms at all
Scale 1
No significant disability despite symptoms: able to carry out all usual duties and activities
Scale 2
Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
Scale 3
Moderate disability: requiring some help, but able to walk without assistance

Scale 4
Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
Scale 5
Severe disability: bedridden incontinent and requiring constant nursing care and attention
Scale 6
Dead

MYOCADIAL INFARCTION (Thygesen et al. J Am Coll Cardiol 2012)

Criteria for acute myocardial infarction:

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Based on the Third universal definition, myocardial infarction will be classified into various types:

Type 1	Spontaneous myocardial infarction	Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2	Myocardial infarction secondary to an ischemic imbalance	In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3	Myocardial infarction resulting in death when biomarker values are unavailable	Myocardial infarction resulting in death when biomarker values are unavailable Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a	Myocardial infarction related to percutaneous coronary intervention (PCI)	Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values > 5 x 99th percentile URL in patients with normal baseline values (< 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required
Type 4b	Myocardial infarction related to stent thrombosis	Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5	Myocardial infarction related to coronary artery bypass grafting (CABG)	Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values > 10 x 99th percentile URL in patients with normal baseline cTn values (< 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Q-wave vs. Non-Q-wave Myocardial infarction:

Q-wave MI will be diagnosed if new pathologic Q-waves (≥25% of the height of the partner R wave and/or ≥0.04 sec in duration) in ≥2 contiguous ECG leads occur. All other MIs not fulfilling the above mentioned criteria will be considered non-Q-wave MI.

URGENT REVASCULARIZATION:

Any PCI or bypass surgery performed for recurrent ischemia that in the Investigators opinion cannot be delayed for more than 24 hours and is defined by the Investigator as a non-elective procedure.

Target Lesion Revascularization:

TLR is defined as any ischemia-driven repeat PCI of the target lesion (including 5 mm proximal and distal to the target lesion) or bypass surgery of the target vessel.

Target Vessel Revascularization:

TVR as any ischemia-driven repeat PCI or bypass surgery of the target vessel. The target vessel consists of target lesion(s) and any additional lesions in the main epicardial coronary artery or branches containing the target lesion

APPENDIX B (DEFINITION OF CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS)

STABLE CORONARY ARTERY DISEASE:

Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia, which are usually inducible by exercise, emotion or other stress and reproducible—but, which may also be occurring spontaneously. Such episodes of ischaemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris). The diagnosis of stable coronary artery disease implies the exclusion of acute coronary syndromes as defined in current guidelines (Roffi et al. 2015)

ANGIOGRAPHIC SUCCESS OF PCI:

Residual stenosis of 30% or less within the stented segment by visual assessment, no evidence of residual dissection or thrombus and final thrombolysis in myocardial infarction (TIMI) flow grade ≥ 2.

DIABETES MELLITUS:

Active treatment with insulin or an oral hypoglycaemic agent on admission

Patients diagnosed with diabetes who are on dietary therapy alone, documentation of an abnormal fasting blood glucose or glucose tolerance test based on the World Health Organization criteria is required.

SMOKING STATUS:

Smoker:	any cigarette smoking in the prior 6 months
Nonsmoker:	no regularly cigarettes smoking at any time (according to the World Health Organization also former smoker that quit smoking for at least 10 years)
Former smoker:	those who had quit smoking at least 6 months before the index PCI.

FAMILY HISTORY OF PREMATURE CAD:

Myocardial infarction, or sudden abrupt death without obvious cause, before the age of 55 in a first-degree blood male relative (parent, sibling, or children related by blood) or before the age of 65 in a first-degree blood female relative.

HISTORY OF HYPERCHOLESTEROLEMIA:

Patients with any one of the following:

1. Prior total cholesterol > 200 mg/dl
2. Prior treatment with a lipid lowering agent for hypercholesterolemia

ARTERIAL HYPERTENSION:

Arterial hypertension is considered to be present when a person's systolic blood pressure is 140 mmHg or greater, and/or their diastolic blood pressure is 90 mmHg or greater on 2 different occasions, or active treatment with antihypertensive drugs.

COMPLEX LESION:

At least 2 criteria of Type B or 1 criterium of Type C has to be met.

CHARACTERISTICS OF ACC/AHA TYPE A, B AND C LESIONS:

Type A Lesions: (high success > 85%; low risk)

- Discrete (<10 mm length)
- Concentric
- Readily accessible
- Non-angulated segment < 45 degrees
- Smooth contour
- Little or no calcification
- Less than totally occlusive
- Not ostial in location
- No major branch involvement
- Absence of thrombus

Type B Lesions: (moderate success, 60 to 85%; moderate risk)

- Tubular (10-20 mm length)
- Eccentric
- Moderate tortuosity of prox. segment
- Moderately angulated, 45-90°
- Irregular contour
- Moderate to heavy calcification

- Total occlusion < 3 months old
- Ostial in location
- Bifurcation lesions requiring double guidewires
- Some thrombus present

Type C Lesions (low success, <60%; high risk)
- Diffuse (> 2 cm length)
- Excessive tortuosity of prox.segment
- Extremely angulated, >90 degrees
- Total occlusion >3 months old
- Inability to protect major side branch
- Degenerated vein grafts with friable lesions

MULTIVESSEL DISEASE:

Presence of angiographically significant lesions (>50% lumen narrowing) in ≥ 2 major epicardial coronary arteries.

NYHA CLASSIFICATION OF HEART FAILURE:

Class I	No limitation of activities; patients suffer no symptoms from ordinary activities.
Class II	Slight, mild limitation of activity; patients are comfortable with rest or with mild exertion.
Class III	Marked limitation of activity; patients are comfortable only at rest.
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

TIMI GRADE FLOW:

- a grading system for coronary flow:

0 No perfusion: No antegrade flow beyond the point of occlusion.

1 Penetration without perfusion: The contrast material passes beyond the area of obstruction, but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.

2 Partial reperfusion: The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel (e.g., the opposite coronary artery or coronary bed proximal to the obstruction).

3 Complete perfusion: Antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery