REVACEPT, AN INHIBITOR OF PLATELET ADHESION IN SYMPTOMATIC CAROTID STENOSIS: A PHASE II, MULTICENTRE; RANDOMISED, DOSE-FINDING, DOUBLE-BLIND AND PLACEBO-CONTROLLED SUPERIORITY STUDY WITH PARALLEL GROUPS

EudraCT Number:
2011-001006-10

Sponsor:	advanceCOR GmbH Fraunhoferstraße 17 D-82152 Martinsried GERMANY
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Coordinating Investigator:	PD Dr. med. Holger Poppert Department of Neurology TU Munich Klinikum rechts der Isar TU München Ismaninger Str. 22 D-81675 München GERMANY

SIGNATURES

Sponsor Representative:

Date: 23.06.2015 Signature:

Prof. Dr. med. Martin Ungerer
(CEO) advanceCOR GmbH

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 advanceCOR, 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.

Coordinating Investigator:

Date: 25 JUN 2015 Signature:

PD Dr. med. Holger Poppert
(Department of Neurology, TU München)

National Coordinating Investigator:

Name: PD Dr. med. HOLGER POPPERT

Institution: Dept. of. NEUROLOGY, TU MÜNCHEN

Date: 25 JUN 2015 Signature:

Principal Investigator:

Name: _____

Institution: _____

Date: _____ Signature: _____

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AMENDMENT HISTORY

Version 1 (03.11.2011)	• Document created

Version 1 (24.11.2011)	• Section 5.2.2:
	  ○ Effective birth control is no longer mandatory for sexually active fertile men who are partners of women of childbearing potential
	• Section 6.1.3:
	  ○ Deletion of IMP labelling example
	• Section 7.1 & 7.1.4:
	  ○ Time frame of visit 4 changed from "treatment + 3 days (-48 hrs /+5 days)" to "treatment + 3 days (-69 hrs /+5 days)"

Version 2 (09.01.2012)	*Changes implemented upon recommendation by the independent ethics committee TU Munich:*
	• Section 1.3 & 5.1:
	  ○ The data safety monitoring board will monitor patient safety more thoroughly
	  ○ The first 10 patients will complete the in-patient phase sequentially at a single study centre
	• Section 10.12.2: Corimmun abstains from holding overall right to veto publications and presentations.

Version 3 (22.02.2012)	*Changes implemented upon recommendation by the regulatory authority:*
	• Section synopsis and 5.2.2:
	  ○ Stricter eligibility criterion for enrolment of hypertensive patients implemented and statement on management of hypertension added
	  ○ Stricter eligibility criterion for ECG abnormalities implemented

Version 4 (16.05.2012)	*Changes implemented upon recommendation by the regulatory authority:* • Section 6.1.6: An in-line filter must be inserted in the syringe pump infusion line during treatment administration. *Administrative changes:* • Section 6.1.7 and 6.2: Emergency unblinding will be performed using the web-based online randomisation tool. • Section 7.2.12: ADP and TRAP concentrations no longer specified due to use of different instruments at individual study sites
Version 5 (26.06.2012)	• *Change of Sponsor from Corimmun GmbH to advanceCOR GmbH*
Version 6 (28.09.2012)	• Section Synopsis, **Fehler! Verweisquelle konnte nicht gefunden werden.**, 7.1, 7.2.12: PFA100 and/or platelet aggregation will be performed at all sites capable of performing the said analysis. • Section 5.1: Sequential treatment of the first 10 patients is not restricted to a single study site. • Section 5.2.2: Patients who have received tirofiban/Aggrastat are eligible for study participation 8 hours after receiving the said anti-platelet agent

Version 7.1 (15.04.2013)	*Substantial changes:*
	• Section synopsis, **Fehler! Verweisquelle konnte nicht gefunden werden.**, 7.2.6 and Appendix A: Amaurosis fugax assessed as secondary endpoint
	• Section synopsis, 5.2.1 and 6.1.7:
	  ○ European Carotid Surgery Trial (ECST) criteria used for grading of carotid stenosis (instead of North American Symptomatic Carotid Endarterectomy Trial criteria)
	  ○ Patients with Amaurosis fugax (subgroup of TIA) included in study population
	  ○ Flow velocity not assessed as inclusion criterion
	• Section 7.2.10: Troponin may be determined instead of CK
	
	Non-substantial changes:
	• Section 1.3: Change of address of DSMB member
	• Section synopsis and 5.1: Wording 'carotid endarterectomy' changed to more general definition of intervention
	• Section synopsis, 5.2.1 and 6.1.7:
	  ○ Wording of exclusion criterion haemorrhagic transformation corrected
	• Section synopsis, 7.1 and 7.2.5: Wound healing complications included in general assessment of adverse events
	• Section 7.2.7: Change of address of TCD core lab
	• Several locations throughout document:
	  ○ thrombocyte function may be analysed by PFA-100 or newer PFA-200 device

Version 7.2 (08.08.2013)	*Non-substantial change:* • Section 8.3.1: Update of SAE fax number
Version 7.3 (12.09.2013)	• *Section 8.1 and 8.3.1: SAE, SAR and SUSAR reporting period for PIs set to 24 hours.*
Version 7.4 (22.07.2014)	• *Section Synopsis and* 5.2.2: Modification of eligibility criteria. • Section 1.3: Change of DSMB meeting interval
Version 8 (22.06.2015)	*Change to exploratory study design due to low incidence of MES (i.e. high screening failure rates) upon recommendation by the DSMB (section Synopsis, section 3, 5 and 9 and minor changes for consistency throughout document).*

SYNOPSIS

Name of Sponsor:	**Coordinating Investigator:**
advanceCOR GmbH Fraunhoferstraße 17 D-82152 Martinsried Germany	PD Dr. med. Holger Poppert Department of Neurology TU München Ismaninger Str. 22 D-81675 München Germany

Title of study:

Revacept, an inhibitor of platelet adhesion in symptomatic carotid stenosis:
A phase II, multicentre, randomised, dose-finding, double-blind and placebo-controlled superiority study with parallel groups.

Protocol identification (code or number):
Revacept/CS/02

OBJECTIVES

Efficacy objectives are:

- Assessment of incidence of microembolic signals (MES) by transcranial Doppler (TCD) examination (before and after treatment)
- Rate of MES per hour (before and after treatment)
- Cerebral lesion analysis by DWI-NMR
- Assessment of neurological status (NIH Stroke Scale)
- Clinical endpoints will be summarised cumulatively i.e. before treatment, after treatment, at 3 months and at 12 months. The following endpoints will be recorded:
    - Rate of all cause death
    - Rate of stroke-related death
    - Any TIA, amaurosis fugax or stroke including haemorrhagic stroke
- Assessment of cardiovascular outcome including myocardial infarction and re-intervention up to 3 and 12 months

Safety objectives are to investigate whether Revacept compared to placebo induces adverse and serious adverse events.

Haemostasis will be closely monitored by assessing:

- laboratory parameters indicating thrombocytopenia and bleeding according to the RE-LY study group criteria
- where feasible: in vitro platelet function with collagen, TRAP and ADP-mediated platelet aggregation and in vitro bleeding time by PFA-100 / PFA-200

Pharmacokinetics of Revacept with respect to drug interaction with other antiplatelet drugs will also be assessed by determining plasma concentrations at various time points after administration of study medication for approximately 20 % of patients.

Methodology:

Multicentre, randomised 2:1, double-blind, placebo controlled, parallel groups, analysis. Blinded evaluation of efficacy and safety endpoints.

Treatment Regime:

Patients suffering from symptomatic carotid artery stenosis, transient ischemic attacks (TIAs), amaurosis fugax or stroke receive either Revacept (single dose) plus antiplatelet monotherapy (Aspirin or Clopidogrel) or monotherapy alone.

Patients receive a single dose of trial medication by intravenous infusion for 20 minutes. Patients are followed up one and three days after treatment, at 3 months and by a telephone interview at 12 months.

Treatment Groups:

150 patients currently receiving standard therapy (aspirin p.o. or Clopidogrel) plus one intravenous injection of:

- Placebo (50 patients)
- 40 mg Revacept (50 patients)
- 120 mg Revacept (50 patients)

Indication, diagnosis and main criteria for inclusion and exclusion:

Main inclusion criteria

- Male and female patients aged >18 years

Diagnosis

- Extracranial carotid artery stenosis (diagnosed by vascular duplex ultrasound peak flow or angiography)

  Lesions with ≥ 50 % stenosis according to the European Carotid Surgery Trial (ECST) criteria

- TIA, amaurosis fugax or stroke within the last 30 days

Main exclusion criteria:

Target disease exception

- NIHSS score > 18
- Recent intracerebral haemorrhage by X-ray computed tomography (CT) or nuclear magnetic resonance (NMR)
- Cardiac cause of embolisation (atrial fibrillation or other cardiac source e.g. artificial heart valves)

Medical history and concurrent disease

- History of hypersensitivity, contraindication or serious adverse reaction to inhibitors of platelet aggregation, hypersensitivity to related drugs (cross-allergy) or to any of the excipients in the study drug
- History or evidence of thrombocytopenia (<30.000/µl), bleeding diathesis or coagulopathy (pathological international normalised ratio (INR) or activated partial thrompoplastin time (aPTT))
- Thrombolysis within the last 48 hours
- Relevant haemorrhagic transformation as determined by CT, NMR or anamnesis
- Oral anticoagulation or dual anti-platelet therapy with aspirin or clopidogrel and other P2Y inhibitors at screening (3 days for dipyridamole extended release; 8 hours for tirofiban/Aggrastat)
- Sustained hypertension (systolic BP >179 mmHg or diastolic BP >109 mmHg)
- History of severe systemic disease such as terminal carcinoma, renal failure (or current creatinine >200 µmol/l), cirrhosis, severe dementia, or psychosis
- Current severe liver dysfunction (transaminase level greater than 5-fold over upper normal range limit)
- Active autoimmune disorder such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis or glomerulonephritis
- Known atrial fibrillation or other clinically significant ECG abnormalities (at present)

Trial duration per subject:

Trial duration per subject will be approximately 6 days. Both treatment and control groups are invited for a 3 months follow up visit and a 12 months follow up telephone interview.

Duration of study: The study was initiated in August 2012. The proposed study end is 2017.

Statistical methods:

Since this is an exploratory study, no formal statistical hypothesis testing will be conducted. Descriptive summary of efficacy and safety data will be provided and the data from this study may be combined and analysed with data from future studies.

LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASA	Acetyl-Salicylic Acid
aPTT	Activated partial thromboplastin time
BfArM	Bundesministerium für Arzneimittel und Medizinprodukte
BMBF	Bundesministerium für Bildung und Forschung
BP	Blood pressure
bpm	beats per minute
CRF	Case Report Form
CRP	C-reactive protein
CT scan	Computerised Tomography scan
CV	Curriculum Vitae
D or d	Day
DAT	Digital Audio Tape
DLR	Deutsches Zentrum für Luft- und Raumfahrt
DQF	Data Query Form
DSMB	Data Safety Monitoring Board
DWI	Diffusion-Weighted Imaging
ECST	European Carotid Surgery Trial
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetate
ESR	Expedited Safety Report
EU	European Union
FSH	Follicle Stimulating Hormone
FWER	Family-wise Error Rate
GCP	Good Clinical Practice
GI	Gastro-Intestinal
GP	General Practitioner
Hr or hrs	hour or hours
ICA	Internal Carotid Artery
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalisation ratio
ITT	intention-to-treat
LMWH	Low Molecular Weight Heparin
MACE	Major Adverse Cardiac Event
MCA	Middle Cerebral Artery
MES	MicroEmbolic Signals
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MRT	Mean residence time
MTD	maximum tolerated dose
NA	Not applicable
NAV	Not available
ND	Not done
NIHSS	National Institute of Health Stroke Scale
OAC	Oral Anti-Coagulant
PP	Per Protocol
PPP	Platelet Poor Plasma
PRP	Platelet Rich Plasma
PT	Prothrombin time
RBC	Red Blood Cell
RRR	Relative Risk Reduction
SAE	Serious adverse event
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TAT	Thrombin-Antithrombin III
TCD	TransCranial Doppler
TIA	Transient Ischaemic Attack
tmax	Time to Cmax
UFH	UnFractionated Heparin
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

1. STUDY ADMINISTRATIVE STRUCTURE

1.1. Sponsor Details

The sponsor of the investigation is:

advanceCOR GmbH
Fraunhoferstraße 17
D-82152 Martinsried
GERMANY

1.2. Coordinating Investigator

The Coordinating Investigator for the investigation is:

PD Dr. med. Holger Poppert
Department of Neurology
TU München
Ismaninger Str. 22
D-81675 München
Germany

Vascular surgery advisor:

Prof. Dr. Hans-Henning Eckstein
Klinik und Poliklinik für Gefäßchirurgie
Ismaningerstr. 22
81675 München
Germany

1.3. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will consist of a statistician together with two independent neurologists who are scientifically well qualified, and who have personal experience of large multicentre studies and data monitoring activities.

Chairman:

Prof. Dr. med. H. C. Diener
Hufelandstr. 55
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Prof. Dr. rer. nat. Ulrich Mansmann
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The DSMB will hold regular meetings to review data concerning safety, efficacy and study performance. Unblinded data describing clinical endpoints, adverse events and laboratory values are to be compiled for these meetings by d.s.h. statistical services. The DSMB will

inform and advise the sponsor of all findings with regard to safety, efficacy and study performance. Review of data can lead the DSMB to a recommendation to the sponsor to stop the study. Minutes of Committee meetings will be recorded and filed. A special charter for the DSMB evaluation will be available. In accordance to GCP-V §13, SUSARS will be reported to the ethics committee, regulatory authority and the DSMB. If serious adverse events are more common in the experimental arm compared to the control arm the risk/benefit consideration will be reassessed. The Committee will inform the sponsor in writing if the frequency of serious adverse events including deaths exceeds 8 percent in one of the groups, and will advise concerning appropriate actions.

The first safety analysis will be performed by the DSMB once 10 patients have completed visit 5. The first 10 patients will be treated sequentially, e.g. only one patient is randomised at a time. The next patient will be randomised only once the first patient has completed visit 5 and no suspected unexpected serious adverse event has occurred (see also section 5.1). In addition, patient randomisation will be stopped by advanceCOR each time a serious adverse event occurs which is unexpected and possibly related to the study medication (SUSAR, see also section 8.3.2). Patient randomization will be resumed only if recommended by the DSMB. Thereafter, the DSMB will perform safety analysis at least annually.

2. INTRODUCTION AND STUDY RATIONALE

Evidence supporting the idea that microemboli accompany transient ischaemic attacks (TIAs), amaurosis fugax and stroke is rapidly accumulating and it is now generally accepted that such microemboli originate at the site of vascular stenosis (Sitzer et al., 1995, Siebler et al., 1992). These microemboli are made up of platelet aggregates that form by two major mechanisms. Firstly, when atherosclerotic plaques ulcerate and rupture, subendothelial tissues expose factors of high platelet-activating potential. Secondly, platelet adhesion and activation at the site of stenosis is greatly facilitated by increased shear stress resulting from blood flow turbulences in atherosclerotic vasculature (Lassila et al., 1990).

In patients with symptomatic stenoses of the internal carotid artery (ICA), a large number of microemboli enter the cerebral circulation, thereby potentially producing a symptomatic clinical event. They can be detected by Transcranial Doppler (TCD) in the form of characteristic microembolic signals (MES) (Ringelstein et al. 1998). 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).

Patients suffering a TIA or stroke are at 30-35 % risk of suffering recurrent stroke within the next 5 years and are advised to undergo vascular surgery in order to reduce the risk of future brain infarction (NASCET Collaborators 1991). In addition to surgical carotid endarterectomy (CEA), administration of antiplatelet agents also favours event free survival and reduces MES frequency in patients undergoing carotid endarterectomy (CEA) (Molloy et al., 1998) and in patients with symptomatic carotid stenosis (Goertler et al., 1999).

Although current antiplatelet agents do reduce the risks for recurrent stroke during and after CEA, their use is associated with potentially life-threatening bleeding complications. It is therefore highly desirable to develop novel therapeutic strategies that selectively inhibit thromboembolisation at the site of vascular stenosis 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 transformation, however, collagen becomes increasingly exposed to the arterial lumen where it triggers platelet aggregation by activating the GPVI receptor on thrombocytes (Nieswandt et al., 2003). By masking collagen exposure to the blood stream at the site of atherosclerotic plaques rather than directly inhibiting thrombocytes, one could prevent local thrombosis without jeopardising systemic platelet functions and coagulation, which is the strategy investigated in this clinical trial. Revacept is a protein that is made up of an Fc (fragment crystallisable) fragment 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).

The mode of action of Revacept was studied in animal models in great detail (Massberg et al., 2004, Schönberger et al., 2008, 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. Furthermore, bleeding times were not increased when Revacept was combined with

conventional antiplatelet agents such as ASA, clopidogrel and heparin. 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 (see Investigator Brochure for more detailed information).

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, 30 male 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. The study presented here aims to demonstrate both safety and evidence of efficacy of Revacept treatment in patients suffering from symptomatic carotid stenosis.

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, maximal pharmacodynamic effects were measured ex vivo, starting at 40 mg, and no drug-related adverse events occurred. Pharmacokinetic studies demonstrated that the area under the curve and maximum concentration proportionally increased with higher dose levels. Because no maximum tolerated dose (MTD) was defined for the adult population and with data generated during preclinical and phase I studies we propose that maximal therapeutic effect is achieved with low to medium doses of Revacept (40 mg and 120 mg).

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. In order to keep this risk low, concomitant oral anticoagulation and antiplatelet drugs other than anti-thrombotic monotherapy with Aspirin or Clopidogrel are prohibited in this study.

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 flue-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 intravenously administered drugs will be excluded from study participation. Furthermore, all patients will remain under medical supervision for 24 hours after receiving study medication.

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. Furthermore, platelet counts and bleeding time will be closely monitored throughout the trial and blood samples for determination of anti-drug antibodies will be collected before and 3 months after exposure to study treatment.

3. STUDY ENDPOINTS

The **efficacy endpoints** are:

- to evaluate whether the incidence of preoperative microembolic signals (MES) is reduced in patients with symptomatic carotid artery stenosis who have been treated with Revacept plus antiplatelet monotherapy (aspirin or clopidogrel) versus antiplatelet monotherapy alone (placebo). MES will be assessed by transcranial Doppler (TCD) examination.(before and after treatment)
- Rate of MES per hour (before and after treatment)
- Assessment of neurological status (NIH Stroke Scale)
- Cerebral lesion analysis by DWI-NMR and correlation to neurological status (before and after treatment)
- Clinical endpoints will be summarised cumulatively i.e. before treatment, one and three days after treatment, at 3 months and at 12 months. The following endpoints will be recorded:
    - Rate of all cause death
    - Rate of stroke-related death
    - Any TIA, amaurosis fugax or stroke including haemorrhagic stroke
- Assessment of cardiovascular outcome including myocardial infarction and re-intervention up to 3 and 12 months

Safety objectives
To assess safety, adverse events will be continuously recorded and be overseen by an independent Data Safety Monitoring Board (see section 1.3).

Safety will be summarised by treatment group and include the following:

- Vital signs
- ECG parameters
- Anti-drug antibody titres
- Reporting AEs including wound healing complications, laboratory abnormalities and use of concomitant medication
- Haemostasis will be closely monitored by assessing:
    - laboratory parameters indicating thrombocytopenia and bleeding according to the RE-LY study group criteria
    - where feasible: in vitro platelet function with collagen, TRAP and ADP-mediated platelet aggregation and in vitro bleeding time by PFA-100 / PFA-200

4. ETHICAL CONSIDERATIONS

4.1. Good Clinical Practice

The investigation will be performed in accordance with the Declaration of Helsinki (1996), 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 advanceCOR GmbH 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.

This study will not use services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

4.2. Independent Ethics Committee (IEC)

It is the responsibility of the Principal Investigator to obtain approval of the investigation plan/ amendments from the IEC and Regulatory Authorities according to local regulatory requirements. The Principal Investigator should file all correspondence with the IEC.

The Principal Investigator is responsible for keeping the IEC informed of the progress of the investigation and of any subsequent modifications to the protocol as deemed appropriate. This should be performed at least once annually. The Principal Investigator must also keep the IEC 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 (or the patient's legally responsible representative), prior to inclusion in the investigation, 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, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available

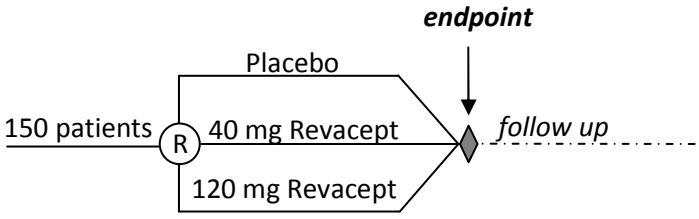
that is relevant to the subject's consent, and should receive IEC approval/favourable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any 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.

5. INVESTIGATIONAL PLAN

5.1. Study Design and Duration

This is a double-blind, placebo-controlled, randomised phase II study. Eligible subjects will be randomised to one of three treatment groups, receive study treatment and undergo endpoint evaluations. Follow ups are scheduled one and three days after treatment, 3 and 12 months.

The first 10 patients will be treated sequentially, e.g. only one patient is randomised at a time. The next patient will be randomised only once the first patient has completed visit 5 and no suspected unexpected serious adverse event has occurred. Prior to randomisation of a new subject, the Investigators must ensure that the patient randomised previously has completed visit 5 and not suffered a suspected unexpected serious adverse event. Once the first 10 patients have completed the sequential phase and the DSMB has recommended continuing the trial, parallel recruitment may start (see also section 1.3).



The study is conducted at a minimum of three study centres which will screen and recruit 150 eligible patients. During the recruitment period, each study centre is expected to provide the capacity and willingness to recruit at least 20 patients. There will be a competitive recruitment of patients, which means that some hospitals will enrol more than 20 patients and some less.

However, if a study centre randomises less than 3 patients in 9 months, further recruitment of patients may be stopped because the quality of a study is dependent on the number of patients per centre. Very few patients in a centre might be related to a higher rate of missing data or patient visits and a higher withdrawal rate.

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 carotid stenosis.

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) Diagnosis:

- Extracranial carotid artery stenosis (diagnosed by vascular duplex ultrasound peak flow or angiography)

  Lesions with ≥ 50 % stenosis according to the European Carotid Surgery Trial (ECST) criteria

- TIA, amaurosis fugax or stroke within the last 30 days

b) Age and sex: Men and women aged >18 years

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

Women who are using 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) 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 the start of study intervention.

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
- Women with a positive pregnancy test on enrolment or prior to investigational product administration.

2) Target disease exceptions

- NIHSS score > 18
- Recent intracerebral haemorrhage by X-ray computed tomography (CT) or nuclear magnetic resonance (NMR)
- Cardiac cause of embolisation (atrial fibrillation or other cardiac source e.g. artificial

heart valves)

3) Medical history and concurrent disease

- History of hypersensitivity, contraindication or serious adverse reaction to inhibitors of platelet aggregation, hypersensitivity to related drugs (cross-allergy) or to any of the excipients in the study drug
- History or evidence of thrombocytopenia (<30.000/µl), bleeding diathesis or coagulopathy (pathological international normalised ratio (INR) or activated partial thrompoplastin time (aPTT))
- Thrombolysis within the last 48 hours
- Relevant haemorrhagic transformation as determined by CT, NMR or anamnesis
- Oral anticoagulation or dual anti-platelet therapy with aspirin or clopidogrel and other P2Y inhibitors at screening (3 days for dipyridamole extended release; 8 hours for tirofiban/Aggrastat)
- Sustained hypertension (systolic BP >179 mmHg or diastolic BP >109 mmHg), hypertensive patients shall be treated in accordance with current guidelines for the management of arterial hypertension
- History of severe systemic disease such as terminal carcinoma, renal failure (or current creatinine >200 µmol/l), cirrhosis, severe dementia, or psychosis
- Current severe liver dysfunction (transaminase level greater than 5-fold over upper normal range limit)
- Active autoimmune disorder such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis or glomerulonephritis
- Known atrial fibrillation or other clinically significant ECG abnormalities (at present)

4) Other Exclusion criteria

- Inability to provide informed consent (except for patient's legally responsible representative)
- Acoustic window that does not allow for TCD recording
- Participation in any other interventional study within less than 30 days prior to screening
- 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)
- Ongoing drug or alcohol abuse

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 advanceCOR GmbH, 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 6 for any reason will be invited to skip to follow up visit 6.

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 advanceCOR with a final report of this SAE or justify why no final report will be provided.

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. Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

6.1.2. Supply of study medication

Manufacturing of drug substance and filling of IMP vials is subcontracted to Glycotope Biotechnology GmbH, Heidelberg, Germany. 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. Please ensure to contact the Monitor or Sponsor of the trial as soon as less than 10 doses of IMP remain, or earlier in case of high recruitment rates.

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 three IMP vials that make up one dose of trial medication for one patient. Each of the three 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 send 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. The investigational product shall be stored in a temperature-controlled freezer at -20 to -90°C in a secured area according to local regulations. 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

advanceCOR GmbH will supply a Drug Accountability Form, to be kept up-to-date by the Investigator.

At the Study Centre

*Used /partially used vials**	Disposal at site according to local policy.
Drugs left unused / expired	Return to advanceCOR GmbH, preferably in the original package, a Drug Return Record Form must be completed.

*Used/partially used vials are accounted for in the Drug Accountability Form and therefore do not need their disposal accounted for separately (nor certificates of disposal) as it is inherent in the 'use' of the vials.

6.1.6. Treatment Administration

Revacept/placebo will be administered once per patient by intravenous injection as described in the handling instructions of the study medication. One patient dose is prepared by combining 3 IMP vials of a single kit box. Please equilibrate all vials of a kit box to room temperature before combining them in a 50 ml syringe pump. An in-line filter rated for syringe pump use must be inserted in the syringe pump infusion line. Infusion of IMP should be for 20 minutes.

6.1.7. Randomisation

Patients will be assigned to a treatment group by web-based online randomisation. Each patient will be allocated to one of the three treatment arms using a minimised randomisation method in order to balance potential prognostic factors between individual treatment arms. The following stratification factors will impact on treatment allocation:

(1) Patient has received anti-platelet therapy with aspirin or clopidogrel prior to screening
- No
- Yes

(2) Patient has received statin therapy prior to screening
- No
- Yes

(3) Degree of carotid stenosis (ECST criteria)
- 50-70%
- > 70%

Once a patient is found to fulfil all eligibility criteria of the study the patient's identification number and details on concomitant medication are submitted to a web-based online randomisation program accessible at:

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

All trial staff involved in patient randomisation will receive their log in data for the program after a short introduction to the system. In order to randomise a new patient, select "*randomise*" in the control panel on the left, enter the patient number (numeric format, including centre specific prefix, e.g. 01-005), select the applicable stratification

factors and click "*randomise*".

In case a reduced set of medication kit boxes is available at the study centre (e.g. due to damage or expiry of trial medication), you may tick option "*reduced set of treatments*", select "*next*", highlight all **unavailable** kit box numbers and then click on "*randomise*".

After successful randomisation of a patient, the web-based online system will send a confirmation email to the person who randomised the patient which contains the patient-specific random kit box number. This confirmation is to be printed, dated, signed and filed in the Investigator Site file.

Please check the number of remaining IMP kit boxes after each patient enrolment and make sure to request additional supplies as soon as less than 10 kit boxes remain, or earlier, in case of high recruitment rates.

6.1.8. Revision of randomisation

Randomisations may be revised if incorrect data have been entered into the web-based randomisation system, if the random kit box number allocated is not available for any reason or if a patient discontinued study participation prior to completion visit 5. In order to revise or reject a patient's randomisation, the following procedure shall be followed:

Revision of patient number

If a wrong patient number was entered into the web-based randomisation system, the entry may be corrected by logging onto the system, choosing "revise randomisation" in the control panel on the left, entering the randomisation number and corrected patient number in the corresponding fields, selecting "change patient-ID" from the drop down menu and providing a reason for the change.

A randomisation must be rejected (and repeated if applicable) for any of the following reasons:

- The medication kit box of the allocated random number is not available for any reason (was damaged, already used etc.)
- A wrong selection was made when entering the patient's stratification factors (degree of stenosis and/or previous Aspirin therapy)
- A patient may be replaced for example because he/she did not complete visit 5

Rejection of randomisation can only be performed by the Sponsor. Please contact the Monitor or the advanceCOR Clinical Development Department as soon as possible.

6.2. Blinding/Unblinding

Emergency unblinding is performed using the web-based online randomisation tool. 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 promptly inform the Monitor or 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).

6.3. Supportive Care

The accompanying medication will encompass the entire spectrum medication for treatment of carotid stenosis, TIA, amaurosis fugax and stroke 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 carotid artery desobliteration. Any required change of concomitant medication in accordance with clinical needs will be documented.

6.4. Treatment Compliance

The study site must keep a record of all study medication dispensed or disposed off throughout the study no matter whether on purpose or accidentally. Subjects who are noncompliant to receiving study medication will be discontinued from study treatment and are offered a follow-up visit including all assessments scheduled for visit 3 and 5.

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. 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.

Procedure	Visit	*Screening*	*Randomisation*	*Treatment (T)*	*T +24 hrs (± 22 hrs)*	*T + 3 d (-69 hrs/+5d)*	*CEA + 24 hrs (± 24 hrs)*	*Follow Up* *T+ 3 m (± 1 m)*	*Follow Up* *T + 12 m (± 1 m)*	*Protocol section*
		1	**-**	**2**	**3**	**4**	**5**	**6**	**7**	
Informed consent		x								4.3
Randomisation			x							6.1.7
Study medication (Revacept or placebo)				x						6
CEA or other intervention						x[f]				7.2.3
CEA / intervention outcome							x[f]			
Anamnesis		x								7.2.1
Concomitant medication		x		x	x	x	x	x		
Physical examination		x[r]		x	x	x[r]	x[r]	x		7.2.2
Adverse events				x	x	x	x	x		7.2.5 and 8
MRS, Barthel Index				x[r]				x		7.2.4
NIH Stroke Scale				x[r]			x[r]	x		
Clinical outcome								x	x	7.2.6
TCD		x			x					7.2.7
Electrocardiogram		x[r]			x		x[r]	x		7.2.8
DWI-NMR		x[a,r]					x			7.2.9
Laboratory Tests	Biochemistry	x[r]			x[r]		x[r]	x		7.2.10
	Haematology / Bleeding	x[r]			x[r]		x[r]	x		7.2.11
	Coagulation	x[r]			x[r]		x[r]	x		7.2.10
	Urinalysis	x[r]			x[r]		x[r]	x		7.2.13
	In vitro bleeding time (PFA100 / PFA200) and aggregation*			x*	x*	x*		x*		7.2.12
	Pregnancy test	x								7.2.14
	Pharmacokinetics (selected patients)			x[b]	x[c]	x[d]		x[e]		7.2.15
	Anti-drug antibodies			x				x		

[r] *routine assessment / blood sampling*
[*] *where feasible*
[a] *eligible patients only*
[b] *drawing times: t0 prior to IMP administration, t 0.5h 30 mins (± 5 mins) after start of IMP infusion, t 6h: 6 h (± 1 hr) after start of IMP infusion*
[c] *drawing time: t24h (± 4 hrs) after start of IMP infusion*
[d] *drawing time: t3d (± 48hrs) after start of IMP infusion*
[e] *drawing time: t3m (± 1month) after start of IMP infusion*
[f] *where applicable*

7.1.1. Visit 1: Screening

Successfully screened subjects may be re-screened if necessary. Visit 1 procedures shall be performed within 24 hours; the order of these procedures shall be as follows:

1) Informed consent must be obtained prior to conducting any procedure that would not have been performed as part of normal subject care
2) date of birth, gender, race, general medical and surgical history (including pre-/ concomitant medication for the last 3 months) will be recorded.
3) physical examination including measurement of body weight, pulse rate and blood pressure and assessment of heart, lung and abdomen will be performed.
4) ECG examination
5) Baseline TCD examination (acoustic window required for eligibility!)
6) clinical biochemistry, clinical haematology (incl. assessment of bleeding according to RE-LY study group criteria), coagulation and urinalysis
7) Urine pregnancy tests are to be performed for all eligible women of childbearing potential (WOCBP).
8) Assessment of eligibility criteria
9) Eligible patients only: Cerebral DWI-NMR (may be performed any time prior to treatment)

Randomisation:

Once all screening examination results are available and indicate that the patient is eligible for the study, patients are allocated to a treatment arm by **stratified randomisation**. Stratification factors are listed in section 6.1.7 p.22.

7.1.2. Visit 2: Treatment

- Physical examination/ vital signs
- Review of concomitant medication
- The trial participant will be given the opportunity to report adverse events (AE) spontaneously, a general prompt will also be given, all adverse events will be followed up until resolution or stabilisation
- Assessment of neurological status (MRS, Barthel Index, NIH Stroke Scale)
- Before administration of study medication, in vitro bleeding time PFA100 / PFA200 and platelet aggregation assay (response to collagen, ADP and TRAP)
- Before administration of study medication, a blood sample for detection of anti-Revacept antibodies will be collected (negative control)
- Pharmacokinetic blood sampling (for approximately 20 % of patients)
  - ***t0*** prior to IMP administration,
  - ***t 0.5h*** 30 mins (± 5 mins) after start of IMP infusion
  - ***t 6h*** 6 h (± 1 hr) after start of IMP infusion
- **Administration of study medication** will be performed by intravenous infusion for 20 minutes; the time of administration must be recorded.

7.1.3. Visit 3: 24 hrs after treatment (between 2 hrs and 46 hrs after treatment)

- Physical examination/ vital signs
- Review of concomitant medication

- Assessment of AEs
- TCD RECORDING
- ECG examination
- clinical biochemistry, clinical haematology (incl. assessment of bleeding according to RE-LY study group criteria), coagulation and urinalysis
- in vitro bleeding time PFA100 PFA200 and platelet aggregation assay (response to collagen, ADP and TRAP)
- Pharmacokinetic blood sampling (for approximately 20 % of patients)
  - ***t24h*** 24 hours (± 4 hrs) after start of IMP infusion

7.1.4. Visit 4: CEA / intervention (3 days after treatment, -69 hrs / + 5 days)

- Physical examination/ vital signs
- Review of concomitant medication
- Assessment of AEs
- in vitro bleeding time PFA100 /PFA200 and platelet aggregation assay (response to collagen, ADP and TRAP)

THEREAFTER CEA SURGERY OR OTHER INTERVENTIONS CAN BE PERFORMED WITHOUT DELAY

- Pharmacokinetic blood sampling (for approximately 20 % of patients)
  - ***T3d*** 3 days (± 48 hrs) after start of IMP infusion

7.1.5. Visit 5: 24 hrs after CEA or other intervention (± 24 hrs)

- Physical examination/ vital signs
- Review of concomitant medication
- Assessment of AEs including wound healing complications
- Assessment of clinical outcome
- ECG examination
- Assessment of interventional outcome and NIHSS
- Cerebral DWI-NMR post intervention (12-72 hrs after intervention)
- clinical biochemistry, clinical haematology (incl. assessment of bleeding according to RE-LY study group criteria), coagulation and urinalysis

7.1.6. Visit 6: follow up 3 months after treatment (± 1 month)

- Physical examination/ vital signs
- Review of concomitant medication
- Assessment of AEs including wound healing complications
- Assessment of neurological status (MRS, Barthel Index, NIH Stroke Scale)
- Assessment of clinical outcome
- ECG examination
- clinical biochemistry, clinical haematology (incl. assessment of bleeding according to RE-LY study group criteria), coagulation and urinalysis
- in vitro bleeding time PFA100 /PFA200 and platelet aggregation assay (response to collagen, ADP and TRAP)
- Pharmacokinetic blood sampling (for approximately 20 % of patients)
  - ***T3m*** 3 months (± 1 month) after IMP infusion
- detection of anti-Revacept antibodies

7.1.7. Visit 7: 12 months telephone follow up (± 1 month)

- Assessment of clinical outcome

7.2. Details of Study Procedures

7.2.1. Review of anamnesis

General medical and surgical history (including pre-/ concomitant medication for the last 3 months) will be recorded at screening.

General risk factors (adapted from SPACE-2):

1) Blood pressure both arms, if difference > 20/10 mm Hg: angiologic assessment performed (n/y)
   Heart rate
2) Height, weight, BMI
3) Physical exercises > 30 min / week (none, 1-2x, ≥ 3x, not known)
4) Lab values glucose (fasting), HbA1c, Cholesterine, HDL, LDL, Triglyceride
5) Smoking habits
   - Non-smoker
   - Ex-smoker / smoker
     - From (year) to (year)
     - No. cigarettes per day
6) Alcohol consumption (y/n), if yes ml/day consumed beer, wine, spirits

7.2.2. Physical examination

Body height will be measured at visit 1. Body weight, heart rate, blood pressure will be recorded at each study visit. The heart rate will taken by feeling the pulse, unless an electrocardiogram is scheduled for the corresponding visit. Blood pressure will be measured once on both arms auscultatorily while the subject is seated, first after 5 minutes of physical and emotional rest. Furthermore, physical examination of heart, lung and abdomen will be performed and any signs of peripheral oedema or ascites will be assessed.

7.2.3. Carotid Endarterectomy

Assessment of CEA (Visit 4)

Detailed CEA specifications will be recorded according to the SPACE-2 study:

- Site of intervention (left/right)
- Anaesthesia (general / local)
- Technique used
- Duration of surgery (minutes)
- Duration of clamping (minutes)
- Degree of residual stenosis
- leakiness at the end of surgery (y/n)

Immediate outcome of CEA will be recorded by assessing:

- Completion of vascularisation procedure
- Discontinuation of vascularisation procedure
  - Prior to carotis opening
  - after probe clamping

Assessment of CEA or intervention outcome (Visit 5)

Adapted from SPACE-2
Complications

- no
- yes
  - Haematoma
  - Other, specify

Further details are given in the CRF formats.

7.2.4. Neurological assessments

See Appendix A for neurological assessment scores. NIH score should be assessed by a certified physician.

7.2.5. Assessment of adverse events

Adverse events will be closely monitored including any unexpected effects on cerebral or myocardial ischemia and bleeding events. Wound healing complications will be documented as part of general adverse event reporting (see also section 8).

7.2.6. Clinical Outcome

Clinical outcome will be summarised cumulatively i.e. before treatment, one and three days after treatment at 3 months and at 12 months. See Appendix B for definitions of clinical events. The following endpoints will be recorded:

- Rate of all cause death
- Rate of stroke-related death
- Any TIA, amaurosis fugax or stroke including haemorrhagic stroke,
- Assessment of cardiovascular outcome including myocardial infarction and re-intervention up to 3 and 12 months

7.2.7. Transcranial Doppler

Central Analysis & Test Run

Each study centre shall send a test dataset to the central core laboratory prior to starting patient recruitment. The core lab will notify the study centre and sponsor of successful completion of a test run. TCD recordings are to be sent to the following core lab for central analysis:

PD Dr. med. M. Ritter
Facharzt für Neurologie
Prinzipalmarkt 11
48143 Münster
Tel.: +49(0) 251 512 55
Fax: +49(0) 251 899 28 61

Central analysis will be performed for both TCD datasets recorded for each patient enrolled (i.e. visit 1 and 3).

There is no need for local analysis of TCD recordings. Both TCD recordings are analysed centrally only.

MES detection by TCD

TCD recordings will be made from the middle cerebral artery (MCA), via the trans-temporal route. Each TCD assessment is recorded for one hour as specified below.
All TCD recordings must be performed under similar conditions, i.e.:

- Same apparatus
- Same position of patient
- System settings

All recordings shall be performed with a DWL TCD machine with single-depth 2-MHz transducers. Standard settings should be used. Machine settings shall be adapted to harmonised consensus guidelines (Ringelstein et al., 1998) and agreed upon by all study centers. For TCD recording, patients are to be placed in a sitting or supine position. The MCS will be identified via transtemporal window and a transducer will be attached using a

standard headset. TCD signals are recorded for one hour. The total number of MES per hour will be analysed.

Spectral display and audio signals will be monitored acoustically and visually online by an experienced observer during all recordings. Audio and visual signals will be recorded onto suitable storage media for central analysis.

MES will be identified visually as predominantly unidirectional short-duration intensity increase accompanied by characteristic acoustic clicking, chirping or moaning sounds. A previously agreed threshold will be set at all participating study centres following validation by analysis of standard reference tapes. MES intensity will be measured in dB and be calculated as the ratio of peak intensity of MES divided by the intensity of the background signal. The same algorithm will be used throughout the study. Central offline analysis of all recordings will be performed using the same machine and same algorithm.

7.2.8. Electrocardiogram (ECG)

A 12-lead ECG will be recorded at rest in supine position: unipolar precordial leads V1-V6 (according to Wilson), bipolar limb leads I, II, III (according to Einthoven), and unipolar limb leads aVR, aVL, aVF (according to Goldberger). The following parameters will be collected:

- Type of rhythm
- PQ interval
- QRS complex
- QT interval
- Assessment of ST-segment deviation

7.2.9. DWI-NMR

The following parameters will be recorded:

- Occurrence of new cerebral lesions from baseline (visit 1) to visit 5
- If possible, number of new cerebral lesions developed between baseline (visit 1) and visit 5

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

Biochemistry

- ALAT/SGPT, albumin, alkaline phosphatase, ASAT/SGOT, blood urea nitrogen, calcium, chloride, creatine phosphokinase / CK-MB or cardiac troponin (selection not to be changes for an individual patient), γ-GT, creatinine, lactate dehydrogenase, glucose, sodium, potassium, total bilirubin, total protein, total cholesterol, triglycerides, uric acid and C-reactive protein (CRP) will be determined.

Haematology

- Haemoglobin, platelet count, haematocrit (where feasible), white blood cell count (WBC) and red blood cell count (RBC), detailed differential hemogram. In case WBC is < 3.500/µl or > 11.000/µl a differential blood count has to be performed i. e., neutrophils, lymphocytes, eosinophils, basophils and monocytes.

Coagulation

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

7.2.11. Bleeding

Assessment of bleeding will be performed at all visits for which Haematology laboratory parameters are scheduled, in addition to adverse event documentation.

Major bleeding is defined as a reduction in haemoglobin level of at least 20 g per litre, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. **Life-threatening bleeding** is a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in haemoglobin level of at least 50 g per litre, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessary surgery. All other bleeding is considered **minor** (Connolly et al., 2009).

7.2.12. Where feasible: PFA 100 / PFA 200 and platelet aggregation

PFA100 / PFA200 and/or platelet aggregation will be performed at all sites capable of performing the said analyses, or within close enough proximity to the advanceCOR laboratory.

Platelet aggregation

In vitro platelet aggregation will be performed after stimulation with collagen, ADP and thrombin receptor activated peptide (TRAP). Details on sample processing, test performance and shipping requirements or logistics will be provided to the individual centres prior to trial initiation.

7.2.13. Urinalysis (in-house)

10 ml urine are to be collected. The following parameters are to be analysed:
Total protein, glucose, blood and pH. In case of any abnormality urinary sediment (where feasible) is also to be determined.

7.2.14. Pregnancy test (in-house)

For women of child-bearing potential (WOCBP) a urine pregnancy test (minimum sensitivity 25 IU/L) will be performed at screening (visit 1). Urine pregnancy tests will be supplied by advanceCOR to the study site.

7.2.15. Pharmacokinetic assessment and detection of anti-drug antibodies (at advanceCOR GmbH)

Pharmacokinetic sampling

For pharmacokinetic assessment, several 2 ml serum blood samples will be collected as specified in section 7.

Blood collection at visit 2 must be performed on the opposite arm of administration of study medication. The time points correspond to the time from starting (not finishing) administration of study medication. Times of administration of study medication and blood sampling must be noted both in the patient's notes and case report form.

Pharmacokinetic measurements are required for approximately 10 patients per treatment group, based on the results obtained in the preceding phase I study. advanceCOR will notify study sites as soon as no further pharmacokinetic samples are required.

Sampling for screening of anti-drug antibodies

For measurement of anti drug antibodies, 2 ml of serum blood will be collected at visit 1 and visit 6.

Preparation and Shipment of Samples

Details on sample processing and shipping requirements and logistics will be provided to the individual centres prior to trial initiation.

Analyses of anti drug antibodies and Revacept pharmacokinetics

Analyses of anti drug antibodies and Revacept pharmacokinetics will be conducted at the advanceCOR GmbH according to validated protocols and SOPs effective at that moment in time.

7.3. Safety Assessments

The safety variables are AE, SAE, data from physical examination, routine laboratory results, ECG, blood pressure, antibody production and heart rate. Signs and symptoms present within 2 weeks of starting therapy (regardless of relationship to current disease) will be obtained at baseline. Study drug toxicities will be assessed continuously. Adverse events will be classified as outlined in section 8 below.

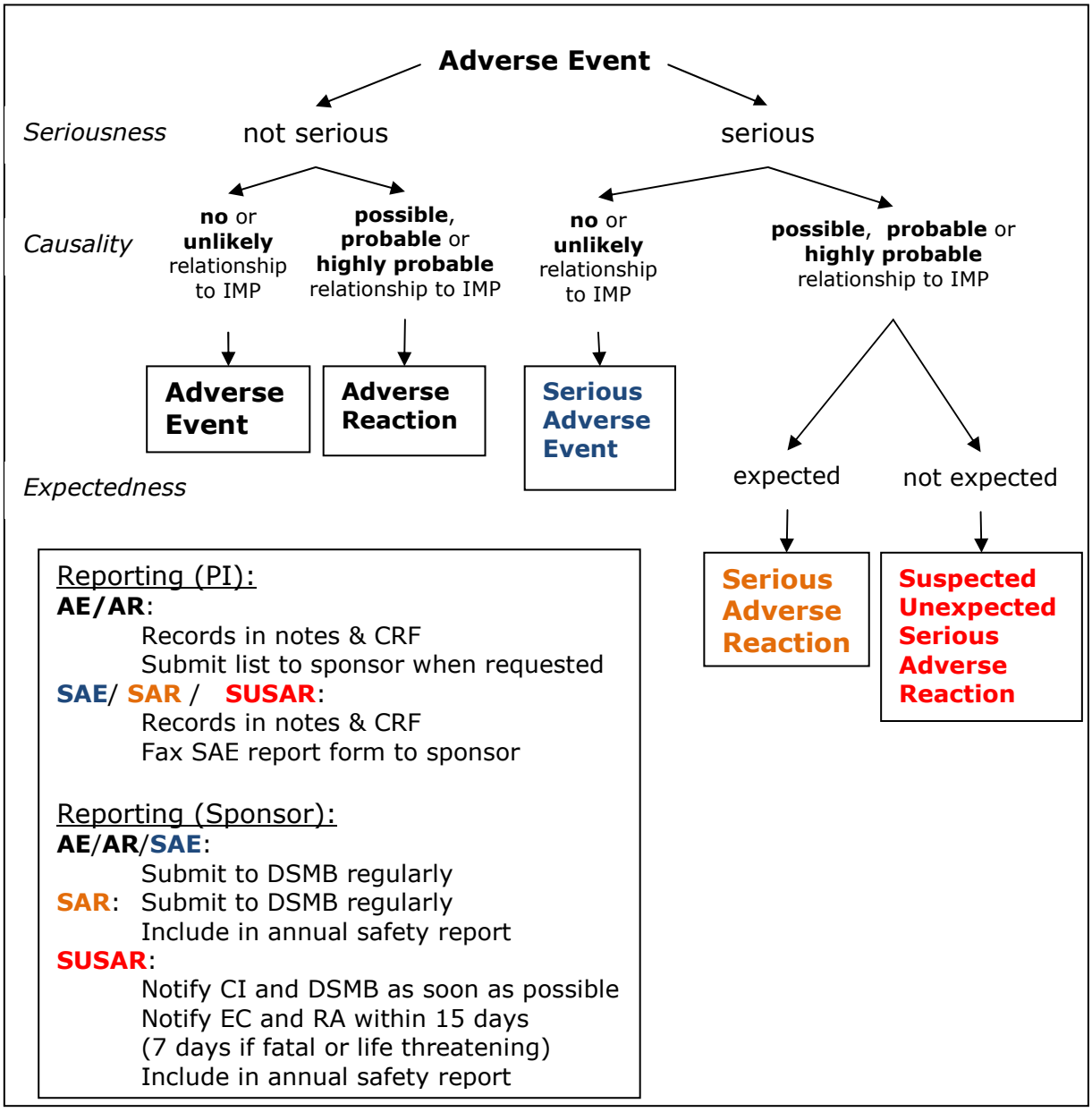
8. ADVERSE EVENTS

8.1. Definitions

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the participation in the clinical trial, whether or not considered related to the investigational product.

Pre-existing conditions, i.e. a disorder present before participation in the clinical trial should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during administration of study medication.

Classifications of Adverse Events and documentation and reporting requirements are visualised in the following scheme alongside the responsibilities of the Sponsor (advanceCOR) and Investigators (see also section 8.3 p. 37).



8.1.1. Serious Adverse Events

A serious AE (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
- 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 [eg, 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 in advanceCOR GmbH clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission 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)

8.1.2. Non-serious Adverse Events

All AEs that are not classified as serious.

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. 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 other 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.
	Hospitalisation or prolongation of hospitalisation	The subject was hospitalised for this AE or subject's stay in hospital was prolonged because 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 outcome:		Date the AE abated. 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:		
	Resolved	The AE is no longer present at any intensity - completely abated.
	Resolved with sequelae	The AE is resolved but residual effects are still present.
	Worsened	The AE is still present but at a heightened intensity. The rule of repetition of AE reporting should be applied.
	Fatal	This AE caused or directly contributed to subject's death.
	Ongoing	The AE is still present at the last contact with the subject.
Relationship to investigational product:		
	None	only applicable when no investigational product was taken or when the subject is taking single-blind placebo, or when the AE can be ascribed with reasonable certainty to another cause.
	Unlikely	there are good reasons to think that there is no relationship, e.g. the AE is a known adverse drug reaction of a concomitant medication, or the same AE does not reappear after re-administration of the investigational product.
	Possible	equally valid arguments can be considered for or against an implication of the investigational product, e.g. the AE : • follows a reasonable temporal sequence from the administration of the investigational product; • follows a known or expected response pattern to the investigational product; • but could readily have been produced by a number of other factors.

Probable	the relationship is likely, e.g. the AE : • follows a reasonable temporal sequence from administration of the investigational product; • follows a known or expected response pattern to the investigational product; • is confirmed by improvement on stopping or reducing the dosage of the investigational product; • could not be reasonably explained by the known characteristics of the subject's clinical state.
Highly probable	there is a strong relationship, e.g. the AE : • follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissues; • follows a known or expected response pattern to the investigational product; • is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the AE on repeated exposure (rechallenge).

8.3. Collection and Reporting

The trial participant will be given the opportunity to report AEs spontaneously. 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, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the appropriate CRF page. The Principal Investigator shall supply the sponsor and Ethics Committee 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 written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure. The Investigator should notify advanceCOR 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 and reported expeditiously to advanceCOR to comply

with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported to advanceCOR within 24 hours after becoming aware of the event by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. 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 (such as 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 to resolution or stabilisation.

SAE Facsimile Transmission:
0049-(0)89-2000 204-20
Local contact: Prof. Dr. med. Götz Münch or Prof. Dr. med. Martin Ungerer (Clinical Research Physicians)

SAE Mailing Address:
advanceCOR GmbH
Clinical Development Department
Fraunhoferstr. 17
D-82152 Martinsried
Germany

8.3.2. Handling of Expedited Safety Reports

advanceCOR will notify Principal Investigators of all SAEs that are suspected (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, 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, important safety recommendations from a study data safety monitoring board, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from advanceCOR, 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 IEC. The Principal Investigator and IEC will determine if the informed consent requires revision. The Investigator should also comply with the IEC procedures for reporting any other safety information.

8.3.3. Non-serious Adverse Events

The collection of nonserious AE information should begin at initiation of study participation, i.e. from the timepoint of obtaining informed consent. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing nonserious AE worsens in its intensity or its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilisation, or reported as SAEs if they become serious (see Section 8.3.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious 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.

All identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF.

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, or be submitted electronically from a central laboratory. In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant 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 ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.6. Pregnancy

Sexually active 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.

Pregnancy testing must also be performed throughout the study as specified the flow chart/time and events schedule (page 24) and the results of all pregnancy tests (positive or negative) recorded on the CRF or transferred electronically.

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 advanceCOR 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 advanceCOR and the outcome information provided once the outcome is known. Completed Pregnancy Report Forms must be forwarded to advanceCOR 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 (e.g. x-ray studies). 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.

Any pregnancy that occurs in a female partner of a male study participant should be also reported to advanceCOR.

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 nonserious AE page of the CRF or SAE paper CRF page.

Classification of cause specific mortality will be performed according to the guidelines listed in Appendix B.

In addition to the regular SAE reporting requirements described in section 8.3.1, any death of any patient randomised into the study must be reported by the Principal Investigator to the Regulatory authority, leading ethics committee as well as the local ethics committee of the study site at which the patient was enrolled as soon as possible.

9. STATISTICAL CONSIDERATIONS

9.1.1. Endpoint Analysis

Endpoint analysis will be performed when 150 patients have completed visit 5 or when advised by the DSMB, whichever occurs earlier. Endpoint analysis includes all data generated from visits 1 to 3.

9.1.2. Additional Analyses

Additional analysis will be performed after the trial has been completed i.e. when the last patient has completed visit 5 or when advised by the DSMB. Additional analyses include all data generated from visit 1-7.

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 (GCP, ICH) and SOPs and working instructions of d.s.h. statistical services effective at that moment in time.

d.s.h. statistical services will document receipt of completed CRFs and perform a general check for legibility, completeness of pages, mandatory values, dates and signatures of Investigators. Subsequently, independent personnel will enter trial data into a validated database system (double data entry) during which incorrect data types and values out of defined ranges will be detected. Changes made in valid data or system operations will be documented by audit trail. Following double data entry, first and second entries will be reconciled using the SAS Compare procedure (data verification).

Data will be checked for plausibility and consistency. Automatic and manual checks required to identify discrepancies will be described in a Data Cleaning Plan. All identified discrepancies are reviewed by data management personnel. Discrepancies can be resolved internally by inspection of the CRF and related data (e.g. if caused by data entry) or by producing Data Query Forms (DQFs) to be sent to the Investigator's site(s) for resolution. Once these queries are resolved and corrections have been implemented in the database, verification and validation procedures will be repeated until no further queries remain.
Subsequently, a 10% quality control audit is performed. For this purpose, a computer program randomly selects 10% of the patients from the database for complete data comparison with the original CRFs.

Furthermore, 100 % of all patients' key data (i .e. adverse events) will be checked and formal quality control will be performed according to d.s.h. statistical services' SOP DM09. Once all Data Quality Control steps are completed and written authorisation of the project leader, data manager and statistician is obtained, the database is locked and records are released for reporting and statistical evaluation

9.2.2. Data Coding

AE coding and coding of concomitant diseases will be performed according to MedDRA Version 13.0 or higher. Concomitant medication will be coded using the ATC code.

9.2.3. Database Lock

The database will be only locked after the following requirements are fulfilled:

- All data have been entered in the database
- Decisions on how individual protocol violations are to be dealt with have been agreed upon
- Written authorisation from the project leader of trial at advanceCOR GmbH has

been granted

9.3. Statistical Procedures

Safety

The number and proportion of patients experiencing each type of event will be summarised per treatment group. Only treatment-emergent events will be included in the analysis (i.e. those that began or worsened after screening (visit 1)).

The incidence and event (or event grouping) will be summarised and compared between treatment groups using Pearson's chi-squared tests.

Blind Review/Final Statistical Analysis Plan

A blinded review of the data shall be performed within the framework of the requirements of the ICH Guideline E9. The Blind Review Report will include the final statistical analysis plan (updated statistical analysis plan) and the final definition of data sets. If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment.

The Blind Review Report will be finalised before the blind will be broken. Formal records shall be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.

9.3.1. 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.

Safety Populations

All Subjects who have received study medication and have had one contact with the Investigator afterwards are analysed for safety.

ITT Population (Full Analysis Set)

For efficacy, all subjects who have had at least one dose of medication will be included in the ITT analysis. The ITT analysis is defined as the first line efficacy 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.

9.3.2. Multicentre Analysis

The analysis of combined centers is the primary analysis of efficacy endpoints. Individual center results will be presented in a graphical overview with effect sizes and confidence intervals for efficacy data.

9.3.3. Missing Values

Rules on how missing values of efficacy variables will be replaced are to be described in the Statistical Analysis Plan.

9.3.4. 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.

9.3.5. Safety Analysis

Physical examinations and vital signs

Findings of physical examinations and changes in vital signs (blood pressure and heart rate) and body weight 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. Serious adverse events will be discussed separately.

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 (d.s.h. Statistical Services), 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

advanceCOR 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, study documentation, informed consent and enrolment of WOCBP.

10.2. Allocation of Responsibilities

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

advanceCOR declares that it has subscribed insurance, 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.

10.5. Study Participation Card an GP Information Letter

Subjects will be given a study participation card containing emergency contact details of their corresponding study site and advanceCOR GmbH 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. Data management and analysis

d.s.h. statistical services GmbH will be responsible for database management during the progress of the study, and for file data analysis. Data will be collected from each participating centre on CRFs supplied by advanceCOR. The CRFs will be monitored and collected by the study monitor and the data entered into the database at d.s.h. statistical services GmbH.

Data management based on GCP refers to the activities defined to achieve safe routines to enter Subject information into a database, efficiently and avoiding errors. The data management routines include procedures for handling of CRFs, database set-up and management, data entry and verification, data validation of database and documentation of the performed activities including information of discrepancies in the process.

The database, the data entry screens and program will be designed in accordance with the study protocol and the CRF. Data recorded in the CRFs and electronically saved data sent from the central laboratories will be entered/ transmitted into the database at d.s.h.

statistical services GmbH and computerised logical checks will be used to ensure the quality of the data (e.g. double data entry). Errors found in the data will be issued on Data Query Forms (DQFs) by d.s.h. statistical services GmbH and the DQFs or queries will then be returned to the study site for resolution. The database will be updated according to the query resolutions and the DQFs will then be archived with the corresponding CRF.

The database will be locked when clean file has been declared. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, the Study Statistician, the Study Data Manager. The breaking of the code will take place after clean file.
The computerised data processing will be the responsibility of d.s.h. statistical services GmbH. Data will be processed in agreement with local legislations.

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 advanceCOR GmbH, the Drug regulatory authority(ies) and for which an approval by the IEC was given. The investigator and advanceCOR 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 CRF 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 advanceCOR GmbH. Every deviation must be documented in the CRF.
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, advanceCOR. 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 CRF.

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:

- advanceCOR GmbH
- IEC for review and approval/favourable opinion

Documentation of approval signed by the chairperson or designee of the IEC(s) must be sent to advanceCOR. 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.

If the revision is an administrative letter, Principal Investigators must inform their IEC(s).

10.7.2. Monitoring

The arrangement for proper monitoring of the trial is the responsibility of the sponsor advanceCOR GmbH. 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 CRFs 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 advanceCOR or its representatives to periodically co-monitor at mutually convenient times during and after the trial, all CRFs and the corresponding source documents. Therefore, advanceCOR or its representatives will have direct access to these records.

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 advanceCOR, IEC review, and regulatory inspection(s), providing direct access to source data/documents. advanceCOR may also perform for-cause monitorings /audits and/or inspections 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 (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 advanceCOR 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 advanceCOR.

Representatives of advanceCOR 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.

advanceCOR GmbH 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 advanceCOR promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to advanceCOR.

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 advanceCOR 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, advanceCOR 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, advanceCOR 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 advanceCOR or by the Principal Investigator, as specified by the applicable regulatory requirement(s).

10.11. Archiving and Data Retention

The Principal Investigator will maintain adequate records for the trial including CRFs, 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 maximum of 15 years. Any further storage has to be agreed separately between the sponsor and the Principal Investigator. He/she will contact advanceCOR 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, copies of CRFs, 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 advanceCOR prior to destroying any records associated with the study.

advanceCOR 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 advanceCOR.

10.11.1. Case Report Forms

advanceCOR will prepare case report forms to record all observations and other data pertinent on each individual treated or entered as a control in the investigation. Data reported in the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained in these source documents.

CRFs supplied by advanceCOR contain all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on separate SAE and Pregnancy Report/Follow-Up Forms. The Principal Investigator will maintain a signature sheet to document signatures and initials of all persons authorised to make entries and/or corrections on CRFs.

The Investigator will keep a subject screening log to document identification of subjects who entered pre-trial screening. The Investigator must submit to advanceCOR or its representatives a completed CRF for each participant.

CRFs will be filled in using a ballpoint pen, and must be legible. Subjects are to be identified by birth date (month and year) and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. advanceCOR cannot interpret a blank answer. Therefore, all fields must be completed. If the data are not available, the Investigator should write "NA" for not applicable, "NK" for not known, and "ND" for not done in all applicable fields. CRFs will be signed and dated by the Investigator as indicated. The Investigator's signature on the CRF attests to its accuracy and completeness.

Corrections must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is a Principal Investigator or Investigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

All supportive documentation submitted to advanceCOR in addition to the CRF, such as laboratory results or hospitalisation records, must be clearly identified with the trial or protocol number, and trial participant number; any personal information, including the trial participant's name, must be removed or rendered illegible to preserve individual confidentiality.

10.12. Publications

10.12.1. Statistical Trial Report

d.s.h. Statistical Services GmbH will prepare a statistical trial report according to the relevant ICH guidelines, on the basis of which advanceCOR 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 advanceCOR. No use should be made of the report before approval by advanceCOR.

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 advanceCOR GmbH. It is agreed that the results of the trial will not be submitted for presentation, abstract, poster exhibition or publication by the Principal Investigator until advanceCOR GmbH has reviewed and commented on such a presentation or publication manuscript. The Principal Investigator agrees that all reasonable comments made by advanceCOR in relation to a proposed publication by the Principal Investigator will be incorporated by the Investigator into the publication. advanceCOR does not hold overall right to veto publications and presentations.

10.13. Investigator Site File

The content of the investigator 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 files will be prepared by and provided to the study sites by advanceCOR GmbH.

10.14. Data Handling and Record Keeping

d.s.h. statistical services GmbH will be responsible for data processing under the supervision of advanceCOR.

CRF 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. The SAS system will be used for the statistical analysis of the data. Regular back-ups of the electronic data will be carried out.

For subjects who signed an informed consent and underwent study specific procedure(s) before entering the treatment phase of the trial, the data collected during the screening period will be entered in the CRF. In case of screening failure, only data on demography, adverse events, and 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.

For subjects who signed an informed consent but terminate study participation prior to the performance of any study procedures, the only data that will be monitored, retrieved, and databased will be data on demography and randomisation/treatment allocation status.

APPENDIX A: SCALES FOR NEUROLOGICAL STATUS

Modified Rankin Scale (MRS):

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Assessment of Barthel Index:

	Score			
	0	**5**	**10**	**15**
Bowels	incontinent	occasional accident (1 per week)	continent	-
Bladder	incontinent or catheterised & unable to manage	occasional accident (max 1/24hrs)	continent for > 7 days	-
Grooming	needs help	independent, face, hair, teeth, shaving	-	-
Toilet use	dependent	needs some help but can do something	independent (on and off, dressing, wiping)	-
Feeding	unable	needs help cutting, spreading butter etc.	independent	-
Transfer	unable	needs help	-	independent
Mobility	immobile	wheelchair independent including corners etc.	walks with help of 1 person (verbal or physical)	independent (may use any aid, e.g. stick)
Dressing	dependent	needs help but ban to half unaided	independent	-
Stairs	unable	needs help (verbal, physical, carrying aid)	independent up and down	-
Bathing	dependent	independent	-	-

APPENDIX B: DEFINITIONS OF CLINICAL EVENTS

Amaurosis fugax	*transient monocular visual loss*
Disabling stroke	*functional disability of 3 or less points on the modified Rankin scale 30 days after symptom onset*
Haemorrhagic stroke	*new focal neurological deficit of vascular origin lasting more than 24 hours, proof of intracranial haemorrhage upon brain imaging*
Ipsilateral stroke	*stroke within the territory of the treated carotid artery*
Ischaemic stroke	*new focal neurological deficit of vascular origin lasting more than 24 hours, absence of intracranial hemorrhage upon brain imaging*
Major adverse event	*Death, stroke*
Major stroke	*initial stroke severity of 4 or more points on the NIHSS*
Minor stroke	*initial stroke severity of 3 points on the NIHSS*
Myocardial infarction	*detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of the following* • *Symptoms of ischaemia* • *ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block)* • *New onset of pathological Q waves in ECG* • *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality*
Procedure-related death	*any death within 30 days of the procedure or mortality resulting from a longer than 30 days hospitalisation because of the procedure*
Procedure-related stroke	*ipsilateral or contralateral stroke that has occurred within 30 days of the procedure*
vascular death	*death due to stroke, myocardial infarction or haemorrhage including deaths not non-vascular*
technical CEA failure	*failure to achieve <30% stenosis one day after CEA*
restenosis	*recurrent stenosis of ≥ 50 %*

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