TRIAL PROTOCOL

MICROVASCULAR AND ANTIINFLAMMATORY EFFECTS OF RIVAROXABAN COMPARED TO LOW DOSE ASPIRIN IN TYPE 2 DIABETIC PATIENTS WITH VERY HIGH CARDIOVASCULAR RISK AND SUBCLINICAL INFLAMMATION

MICROVASC-DIVA

Sponsor
GWT-TUD GmbH
Blasewitzer Straße 43
01307 Dresden
Germany

Coordinating Principal Investigator
PD Dr. Frank Pistrosch
GWT-TUD GmbH, Studienzentrum Prof. Hanefeld
Blasewitzer Str. 43,
01307 Dresden

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SIGNATURES OF SPONSOR AND COORDINATING PRINCIPAL INVESTIGATOR

By my signature, I agree to supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable legislation governing the conduct of clinical studies.

Sponsor

Claus-Peter Held

Dresden 16/07/16
place and date

Coordinating Principal Investigator

PD Dr. Frank Pistrosch

Dresden, 15 JUL 2016
place and date

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Investigators

Name of investigator	date and signature
Name of investigator	date and signature
Name of investigator	date and signature
Name of investigator	date and signature

SYNOPSIS

Sponsor	GWT-TUD GmbH Blasewitzer Straße 43 01307 Dresden Germany
Coordinating Principal Investigator	PD Dr. med. Frank Pistrosch
Title of the clinical trial	Microvascular and antiinflammatory effects of Rivaroxaban compared to low dose aspirin in type 2 diabetic patients with very high cardiovascular risk and subclinical inflammation
Indication	Rivaroxaban 5 mg b.i.d vs. aspirin 100 mg qd in patients with type 2 diabetes and very high cardiovascular risk
Phase	III b
Type of trial, trial design, methodology	prospective, comparative active controlled, randomized, 2 parallel arms, open study
Number of subjects	188 patients in (94 patients each arm)
Treatment Groups	Arm A (treatment group): Rivaroxaban 5 mg b.i.d Arm B (control group): ASS 100 mg qd
Treatment period	20 weeks + additional 32 weeks (extension study for 80 patients)
Time plan	First patient first visit (FPFV): April 2015 Last patient first visit (LPFV): July 2017 Last patient last visit (LPLV): August 2018 Database Lock: December 2018 Final study report: April 2019

Study objectives

Primary objectives

Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 20 weeks treatment between rivaroxoban and aspirin therapy
Additionally the difference of arterial stiffness after 52 weeks treatment (extension study) between rivaroxoban and aspirin therapy will be evaluated.

Secondary objectives

- change of peripheral skin microcirculatory function (measured by laserdopplerfluxmetry; LDF) after 20 and 52 weeks of treatment
- LDF baseline
- LDF after ischemia (endothelial function)
- arterial stiffness measured by Mobilograph (IEM Inc.) after 20 weeks of treatment
- laboratory markers for endothelial function
- VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin, P-Selectin, CD40-L
- Microalbuminuria, eGFR
- composite of biomarkers of inflammation
- hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes, MPO, IL-6, IL-8
- side effects: major bleeding according to ISTH, symptomatic thromboembolic events
- metabolic marker: HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C
- coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1 + 2, D-Dimer, Protein C, Protein S, TAT, Quick, aPTT
- cardiovascular marker: NT-proBNP, hs-TnI, GDF-15, MR-ANP

Additional secondary objective for extension period:

- Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 52 weeks treatment

Explorative Study Objective(s)

assessment of platelet activation and measurement of mitogenic potential

Study end points	**Primary variable** ▪ change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at 20 weeks **Additional primary variable for extension period:** ▪ pulse wave velocity at EOT after 52 weeks
Study end points	**Secondary variables** ▪ change of the area under the postischemic FBF curve over 10 cycles of intermittent venous congestion (compared to baseline) after 20 weeks and EOT Extension ▪ ▪ maximal postischemic skin blood flow (arbitrary units) during reactive hyperaemia after 5 min of forearm ischemia at 20 weeks and EOT Extension using LDF ▪ change of postischemic skin blood flow (compared to baseline) using LDF ▪ Pulse wave velocity at 20 weeks compared to baseline ▪ laboratory parameter (see above) at 20 weeks and EOT Extension **Additional secondary variable for extension period:** ▪ change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at EOT after 52 weeks (EOT Extension)

Safety Parameter	**Safety Parameter** ▪ major bleeding defined as clinically overt and associated with one of the following: - reduction of hemoglobin level of 2 g/L or - required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal, in accordance with the recommendation of the International Society on Thrombosis and Haemostasis (ISTH). ▪ clinically relevant non major bleeding defined as at least one of the following: - spontaneous skin hematoma of at least 25 cm - spontaneous nose bleeding of more than 5 minutes duration - macroscopic hematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours - spontaneous rectal bleeding (more than spotting on toilet paper) - gingival bleeding for more than 5 minutes - bleeding leading to hospitalization and/or requiring surgical treatment - bleeding leading to a transfusion of less than 2 units of whole blood or red cells - any other bleeding event considered clinically relevant by the investigator
Medical condition	**Medical condition or disease to be investigated**: Patients with type 2 diabetes and stable cardiovascular disease (CVD) and low grade inflammation

In-/Exclusion criteria	Principal inclusion criteria: ▪ type 2 diabetes duration between 2 and 20 years ▪ two or more components of metabolic syndrome: - HDL cholesterol < 1.0 mmol/L (in males) or < 1.3 mmol/L (in females) - Elevated triglycerides (> 1,7 mmol/L) - Elevated blood pressure (>130 mmHg systolic and/or >85 mmHg diastolic or antihypertensive treatment) - Elevated waist circumference (>102 cm in males , > 85 cm in females) ▪ or at least one of the following - carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or - left ventricular hypertrophy or - increased UACR in the absence of other renal diseases than diabetic nephropathy ▪ increased hsCRP (> 2 mg/l but < 10 mg/l) at or within 6 months prior to screening and/or increased PAI 1 (> 15 ng/ml) at or within 6 months prior to screening(the historical hsCRP or PAI 1 value can be used only if the patient was in stable conditions regarding the concomitant diseases and statin therapy since the time point of measurement) ▪ stable treatment with statines (if tolerated/clinically indicated) ▪ age 40 – 75 years

	Principal exclusion criteria: ▪ major CV event with need for oral anticoagulation or platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry ▪ sustained uncontrolled hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg ▪ hypersensitivity to the active substance or to any of the excipients ▪ active clinically significant bleeding ▪ lesion or condition, if considered to be a significant risk for major bleeding ▪ concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) ▪ hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C ▪ chronic renal failure with eGFR < 15 ml/min (MDRD formula) ▪ Pregnant or breast-feeding woman and woman without adequate method of contraception.
Measurement of results	**Venous occlusion plethysmography for assessment of FBF:** Endothelium dependent vasodilation of resistance vessels will be assessed in both arms simultaneously using strain-gauge venous occlusion plethysmography (Gutmann Medizinelektronik, Eurasburg, Germany or Hokanson Pletysmograph EC6). Endothelium dependent dilation of forearm resistance vessels will be stimulated in one arm by suprasystolic occlusion for 5 min and subsequent postischaemic release of endogenous vasodilators. The contra lateral arm serves as control.
	Laser Doppler Fluxometry (LDF): The technique of micro-lightguide spectrophotometry and laserdopplerfluxmetry will be used to measure microvascular skin blood flow and postcapillary tissue oxygenation (sO2) at the lower forearm. LDF skin probes will be placed at the lower forearm and on the thenar surface of the left hand in between the phalanx of the thumb and the metatarsale of Dig II, directly adjacent to the muscle abductor pollicis. Microvascular blood flow and post-capillary sO2 will be measured in parallel in a tissue depth of 2 mm and 8 mm. Via a cuff on the upper arm a supra-systolic occlusion will be induced for 4 minutes, and thereafter, the postischaemic microvascular blood flow and sO2 will be recorded as a measure of microvascular endothelial function in the skin.

	Pulse wave velocity and arterial stiffness: Measurements will be performed using the Mobil-O-Graph device (IEM Inc., Stolberg, Germany). This device allows the non-invasive oscillometric analysis of blood pressure and pulse wave over 24 hours. Based on pulse wave analysis we calculate the aortic augmentation index as marker of arterial stiffness and pulse wave velocity. The Mobil-O-Graph device has been validated against gold standard procedures such as applanation tonometry (SphygmoCor, AtCor Inc.).
Measurement of results	**Assessment of platelet activation and mitogenic potential** Platelet activation will be assessed by measuring platelet derived microparticles (PMP) by separating platelet poor plasma from platelet rich plasma. Subsequently, analysis of platelet microparticles and their mitogenic potential will be performed after sample thawing. PMP will be measured after staining with anti-GP1b antibodies by fluorescence-activated cell sorting (FACS). In addition, magnetic beads linked with anti-GP1 b antibodies will be used to extract PMP from platelet poor plasma. Extracted PMP will then be added to human vascular endothelial cells (HUVECS) and migration (Boyden chamber) as well as proliferation (BrdU) of HUVECs will be assessed with and without PMP with samples from patients undergoing platelet inhibition or rivaroxaban treatment. Platelet rich plasma will be used to measure platelet activation by cGMP dependent phosphorylation of vasodilator-stimulated phosphoprotein (VASP) at Ser-157 which will be detected by flow cytometry.
Statistical methods	**Efficacy:** The statistical analysis will be done in the intention to treat and per protocol set. The primary parameter will be the maximum FBF at 20 weeks (assessed with venous occlusion plethysmography after forearm ischemia) controlling for baseline FBF and the Pulse Wave Velocity (PWV) at EOT (extended treatment period after 52 weeks) assessed with a sphygmograph (Mobilograph®, IEM) using an analysis of covariance (ANCOVA). Independent t-test will be used to test the parameters between the groups at the time point as well as the change between baseline and 20 weeks of treatment. Additionally, measurements will also be compared to an extended treatment up to 52 weeks (EOT Extension). **Safety:** Analysis of bleeding events and safety parameters is required.

Statistical methods	**Sample Size Estimation:** The first primary variable is change of forearm blood blow with venous occlusion plethysmography (ΔFBF) after forearm ischemia after 20 weeks treatment. The sample size calculation is based on the following assumptions: $H0: \Delta FBF_{Riva} \leq \Delta FBF_{ASS}$ $H1: \Delta FBF_{Riva} > \Delta FBF_{ASS}$ ▪ Type I error: α = 0.05, one-tailed t-test for independent samples ▪ Power: 1-ß = 0.90 ▪ Estimated dropout rate : 25 % ▪ Minimum of expected clinical relevant difference between the groups in changes of maximal forearm blood flow (ΔFBF) = 1.2 ml/100ml with an estimated standard deviation (SD) of σ = 2.4 ml/100ml [Pistrosch, F. et al. Diabetes Care 27: 484-490, 2004] Sample size should be N = 188 Patients ($N_{1/2}$ = 94 patients per arm) for a valid number of 141 patients for per protocol analysis. This sample size may also provide enough power for further analyses. Additionally, the second primary variable is the difference of PWV between treatment groups at EOT Extension (after 52 week of treatment). The sample size calculation is based on the following assumptions: $H0: PWV_{Riva} = PWV_{ASS}$ $H1: PWV_{Riva} \neq PWV_{ASS}$ ▪ Type I error: α = 0.05, t-test for independent samples ▪ Power: 1-ß = 0.80 ▪ Estimated dropout rate : 20 % ▪ Minimum of expected clinical relevant difference between the groups in PWV = 0.7 m/s with an estimated standard deviation (SD) of σ = 1.0 m/s Sample size should be N=80 patients (40 patients per arm) for a valid number of 66 patients for per protocol analysis. In summary the necessary sample size would be N=188 patients for the study up to week 20 including 80 patients for the extension up to week 52.
GCP conformance	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.
Financing	GWT-TUD GmbH with support of Bayer Vital GmbH

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ABBREVIATIONS

ACS	Acute coronary syndrome
ADR	Adverse drug reaction
AE	Adverse Event
ALT	alaninetransferase
AMG	Arzneimittelgesetz
BfArM	Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*)
b.i.d.	bis in die (lat.) – twice a day
CPI	Coordinating Principal Investigator (*Leiter der klinischen Prüfung*)
CV	Cardiovascular
CVD	Cardiovascular disease
eCRF	electronic Case Report Form
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full analysis set
FBF	Forearm bloodflow
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
ISF	Investigator Site File
ITT	Intent-to-treat analysis
LDF	Laser Doppler Fluxometry
PMP	Platelet derived microparticles
PPS	Per protocol set
qd	quaque die (lat.) - daily
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAS	Safety analysis set
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
UFH	unfractioned heparine
ULN	upper limit of normal
V1-7	visit 1 to 7

1 Introduction

Type 2 diabetes as part of the metabolic syndrome is associated with dyslipidemia, elevated blood pressure, a prothrombotic environment and a proinflammatory state. This cluster of risk factors accelerates the development of micro- and macrovascular complications (1). There is increasing evidence that patients with type 2 diabetes and high cardiovascular risk have an activated coagulation pathway and deteriorated fibrinolysis which resulted in an increased production of fibrin which might be involved in the initiation and progression of microvessel disease and macrovascular complications(2), (3).

Rivaroxaban, a factor Xa inhibitor was shown to be as effective as warfarin in the prevention of stroke or embolism in patients with non-valvular atrial fibrillation. At the end of 2011, Rivaroxaban was approved by the FDA and the EMA for the prevention of thromboembolism in patients with non-valvular atrial fibrillation(4).

The ATLAS trial in patients with acute coronary syndrome was a large international randomized study to evaluate efficacy and safety of rivaroxaban vs. placebo on top of background medication with low dose aspirin and clopidogrel or ticlopidine. Rivaroxaban significantly reduced the risk of cardiovascular (CV) death, myocardial infarction or stroke but had no significant effect on fatal bleeding (5). Recently, another large multi-center phase III study has been started in patients with stable cardiovascular disease to compare the efficacy of rivaroxaban alone (or in combination with aspirin) vs. aspirin alone on prevention of further heart attacks, stroke or cardiovascular death (COMPASS trial, www.clinicaltrials.gov, NCT01776424).

These large mega-trial in high risk patients support our working hypothesis that secondary prevention with rivaroxaban low dose therapy is superior for microvascular circulations and – on the long run - for CV outcome and mortality in patients with type 2 diabetes and high cardiovascular risk vs. low dose aspirin still used in daily practice. As in the COMPASS study rivaroxaban 5.0 mg twice daily will be used for this exploratory study.

Moreover there is an increasing evidence from mechanistic studies that beyond the anti-coagulatory action, inhibition of factor Xa might have some additional anti-inflammatory effects and that the treatment with factor Xa inhibitors might evolve some beneficial effects in the microcirculation (6). Microcirculation is a critical pathway for diabetes related diseases such as retinopathy and nephropathy. Even more important diabetic CVD is characterized by multi-vessel disease including small vessels.

Studies with Rivaroxaban or the direct thrombin inhibitor Ximelagatran in comparison to antiplatelet therapy demonstrated an increased efficacy regarding cardiovascular end points but a small increased risk of bleeding (7). This study will analyze surrogate parameters for CV-outcome in a very high risk population with type 2 diabetes.

The goal of this study is to evaluate microcirculatory and anti-inflammatory effects of Rivaroxaban compared to low dose Aspirin in type 2 diabetic patients with high cardiovascular risk according to national guidelines and documented subclinical inflammation Thus the results will be of high

clinical relevance. Forearm blood flow (FBF) measurement serves as gold standard technique for the assessment of endothelial function in resistance vessels and provides sufficient reproducibility and validity as documented in the literature (8). Furthermore there was a good correlation between impaired FBF and subsequent cardiovascular events (9). Therefore FBF for assessment of microvascular function is able to predict macrovascular events.

Previous studies demonstrated a fast response of forearm blood flow to interventions (10) however; forearm blood flow is a marker of endothelial (dys)function and did not measure structural changes of large conductive arteries or the microvascular bed. In contrast to forearm blood flow changes which occur within a few weeks after an intervention, these structural adaptation of the vascular wall usually require a longer time span.

There are few investigational studies of microvascular skin blood flow in patients with type 2 diabetes which described significant changes during treatment with glucose lowering drugs after 36 weeks (11). However; an extrapolation from the capillary bed to structural changes of large arteries should be difficult due to the different anatomy of the vascular wall. Pulse wave velocity (PWV) as marker of arterial stiffness is an independent predictor of cardiovascular events and mortality (12, 13).

Changes of PWV during medical intervention usually required a longer time span. This had been demonstrated in studies with antihypertensive agents (14) as well as in studies with lipid lowering medication (15) which required treatment periods of at least 12 months to demonstrate an improvement of PWV. We believe that a structural remodeling of the vascular wall in the present investigation also needs that period of time.

2 Objectives of the clinical trial

Objectives of this clinical trial are the in vivo assessment of microvascular function using different non-invasive techniques and the in vitro assessment of biomarkers of endothelial damage, inflammation and coagulation/fibrinolysis before and after treatment with either aspirin or rivaroxaban in type 2 diabetic patients with high cardiovascular risk and inflammation. Furthermore possible functional interactions between mononuclear blood cells and platelets as well as expression of mRNA (and protein) within these cells before and after treatment in vitro will be assessed.

2.1 Rationale for the clinical trial

Type 2 Diabetes is associated with an increased risk of CV events which might be attributable not only to macrovascular damage (e.g. atherosclerotic plaques) but also to microvessel disease. Previous studies demonstrated a procoagulant state associated with low grade inflammation in these patients (3). Furthermore there are disturbances of blood flow due to increased viscosity and deteriorations in endothelial function with diminished release of endogenous vasodilators

(10). As a result, tissue oxygenation and blood supply to peripheral tissues are reduced. Current treatment with aspirin or other antiplatelet drugs have been demonstrated to reduce the risk of macrovascular events due to the prevention of thrombus formation on atherosclerotic plaques in the case of secondary prevention. However, antiplatelet therapy has little or no effect on microvascular disease (16, 17) (11). The recent introductions of non-vitamin K dependent anticoagulant drugs have increased treatment options for prevention of thromboembolic events after deep venous thrombosis or in patients with atrial fibrillation. In addition a large prospective multicentre study - the ATLAS trial - also demonstrated a risk reduction of CV events in patients with ACS in addition to standard of care antiplatelet therapy (18)(5). This might be due to improved microvascular function and blood supply to microvascular beds. A measurement of microvascular functions in patients receiving non-vitamin K dependent anticoagulant drugs have not been evaluated so far. Therefore the present pilot study has to be conducted.

2.2 Primary objective

Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 20 weeks treatment between rivaroxoban and aspirin therapy

Additionally the difference of arterial stiffness after the end of the extension study (week 52) between rivaroxoban and aspirin therapy will be evaluated.

2.3 Secondary and other objectives

- change of peripheral skin microcirculatory function (measured by laserdopplerfluxmetry; LDF) after 20 and 52 weeks of treatment
- LDF baseline
- LDF after ischemia (endothelial function)
- arterial stiffness measured by Mobilograph (IEM Inc.) after 20 weeks of treatment
- laboratory markers for endothelial function
- VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin, P-Selectin, CD40-L
- Microalbuminuria, eGFR
- composite of biomarkers of inflammation
- hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes, MPO, IL-6, IL-8
- side effects: major bleeding according to ISTH, symptomatic thromboembolic events
- metabolic marker: HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C
- coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1 + 2, D-Dimer, Protein C, Protein S, TAT, Quick, aPTT
- cardiovascular marker: NT-proBNP, hs-TnI, GDF-15, MR-ANP

Additional secondary objective for extension period:

- Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 52 weeks treatment

2.4 Measurement of mitogenic potential and assessment of platelet activation

The rationale of this study is to clarify whether oral non-vitamin K dependent anticoagulant drugs are able to improve microvessel function and hence microcirculation and tissue oxygenation in patients with a disturbance of endothelial function. Furthermore we would like to clarify whether these drugs act only via inhibition of coagulation or whether there are additional effects on inflammation or platelet function. There are no comparable studies in humans so far in the literature and the study procedures (non-invasive techniques for assessment of endothelial function) bear no additional risk. Venous blood samples will be taken at screening, baseline and end of treatment, the whole amount of blood which is required for biochemical tests is about 150 ml.

2.5 Risk-Benefit-Assessment

The major risk of oral anticoagulation is the risk of bleeding. This risk is dose dependent and exceeds (in combination with aspirin) the bleeding risk of aspirin 100 mg/d (alone) by a factor of 2 (ATLAS trial) (13). The bleeding risk is lower than the bleeding risk with Vitamin K dependent anticoagulant drugs, especially in the dose of 5 mg b.i.d. (7). Unfortunately there are no direct comparisons of the bleeding risk between aspirin 100 mg and rivaroxaban5 mg b.i.d. so far in the literature. The results of the COMPASS trial, which is still recruiting will provide further data on this issue.

Since all patients of our planned investigation have a high risk for cardiovascular disease a primary prevention of CV events with aspirin 100 mg is recommended by several guidelines (19) however, this recommendation is not so strong as the indication for aspirin in the case of secondary prevention. In Germany the therapeutic costs for a primary prevention with aspirin 100 mg even in high risk patients are not covered by general health insurance, therefore a lot of patients do not get a prescription of this medication. The inclusion of these patients with a high CV risk but without a major CV event in medical history would offer the possibility to cover high risk patients with a recommended treatment for the duration of the study. To minimize the bleeding risk for the patients we will conduct four safety visits during the treatment of 20 weeks of study medication and will not include patients with an increased risk of bleeding as stated in the exclusion criteria.

In conclusion there is scientific evidence, that patients with a very high cardiovascular risk in a state of primary prevention and with a low risk for bleeding should be treated. The standard recommended treatment today is low dose aspirin, but in our point of view considering the expected advantages of rivaroxaban at a low dose would outweigh the possible increased risk of bleeding.

3 Organizational and administrative aspects of the trial

3.1 Sponsor

GWT-TUD GmbH
Blasewitzer Str. 43
01307 Dresden
Germany

3.2 Coordinating Principal Investigator (*Leiter der klinischen Prüfung* according to German Drug Law)

Coordinating Principal Investigator

PD Dr. Frank Pistrosch

GWT, Study centre, Blasewitzer Str. 43, 01307 Dresden

Tel.: +49 351 4400580

Fax No: +49 351 4400581

3.3 Monitoring

Monitoring will be conducted in accordance with ICH-GCP E6 (5.18). Monitoring will be performed by the sponsor GWT-TUD GmbH.

3.4 Datamanagement

Datamanagement will be performed by the sponsor GWT-TUD GmbH.

3.5 Statistics

Statistic will be performed by the sponsor GWT-TUD GmbH.

3.6 Data and Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) of independent experts will be set up. It will consist of two physicians and one statistician who are not involved in the conduct of the trial. The task of the DSMB is to oversee the safety of the trial subjects in the clinical trial by periodically assessing

the safety and efficacy of the trial therapy and to monitor the integrity and validity of the data collected and the conduct of the clinical trial.

Throughout this process of surveillance, the DSMB will provide the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected. The data necessary for the DSMB to fulfill this function will be provided by the sponsor as determined by the DSMB charter.

3.7 Investigators and trial sites

The multicenter trial is planned to be conducted in up to 7 national trial sites in Germany by investigators with special expertise in the field of indication.

3.7.1 Requirements for investigators and trial sites

The trial site will be required to have an investigator with at least 2 years experience in conducting clinical trials according to GCP as well as a substitute with comparable qualifications. The site must have a pool of suitable patients who can be recruited for the study.

All investigators must be qualified physicians. Each physician must supply his or her curriculum vitae (updated), a financial disclosure and certificates of GCP experiences for the TMF. All investigators must have skills in the assessment of endothelial function using prespecified techniques and should be familiar with anticoagulant treatment.

Investigators also must

- know main features of the law in Germany ("*Arzneimittelgesetz*") as well as legal and scientific basics of clinical trials
- know and sign the study protocol.

If any of the investigators are not physicians, these must be listed with reasons why they are suitable to be involved in the trial.

All investigators must sign the protocol signature sheet before subject recruitment and treatment may start. Likewise, all protocol amendments/integrated protocols must be signed and dated by the investigators before coming into effect.

3.8 Other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the center will be available in the center's investigator site file and the trial master file (TMF) of the sponsor.

3.9 Financing

The clinical trial will be financed by the sponsor GWT-TUD GmbH with a support of Bayer Vital GmbH. Bayer will also provide the IMP Rivaroxaban (Xarelto® 2.5 mg).

4 **Trial conduct**Time plan

First patient first visit (FPFV):	April 2015
Last patient first visit (LPFV):	July 2017
Last patient last visit (LPLV):	August 2018
Database Lock	December 2018
Final study report:	April 2019

4.2 Design overview

This will be a multi center, open-label, controlled study with two treatment arms running in parallel. A total of 188 patients of both genders and older than 18 years with type 2 diabetes and documented high cardiovascular risk and low grade inflammation will be randomly assigned to one of two treatment groups:

4.2.1 Treatment groups

Arm A:treatment group **Rivaroxaban**	Patients will receive Rivaroxaban 5 mg b.i.d. for the duration of 20 weeks. Additionally, 80 patients of the study population will continue to receive the Rivaroxaban 5 mg b.i.d. for a duration of 52 weeks (extension treatment).
Arm B: control group **Aspirin**	Patients will receive treatment with Aspirin 100 mg q.d. for the duration of 20 weeks. Additionally, 80 patients of the study population will continue to receive the Aspirin 100 mg q.d. for a duration of 52 weeks (extension treatment).

TABLE 1: TREATMENT GROUPS

7 study visits will be performed during the study. Subjects are obliged to come to the study center for 5 visits. Visits will take place at week –2 (screening – V0), day 0 (randomization/baseline – V1), at week 2 (V2), 4 (V3), 8 (V4), 12 (safety/compliance – V5) and week 20 (end of treatment for the first study period with vascular function test – V6).). Visit 3 and Visit 5 will be conducted as a telephone visit.

Additionally, 80 patients of the study population will perform 7 additional visits during the extension period. These visits will start after week 20. Patients attending the extension period will perform overall 14 study visits for 8 of these visits they will come to the study center whereas overall 6 visits are performed as telephone visits. The additional visits will take place at week 24

(V7), week 28 (V8), week 32 (V9), week 36 (V10), week 40 (V11), week 44 (V12) and week 52 (end of treatment extension - V13). Visit 7, 9, 11 and 12 will be conducted as a telephone visit.

Measurements of FBF, LDF and pletysmography at baseline-visit, visit week 20 (V6) and EOT-visit (V13) can be done up to 3 days after the visits in the corresponding study location that provides these measurements. Patients will be informed of the procedure by the physician.

4.2.2 Visit schedule

4.2.2.1 Visit schedule for 20 Weeks of treatment

Visit specification	V0 screening	V1 baseline	V2	V3 telephone	V4	V5 telephone	V6
week	day -28	day 0	2	4	8	12	20
timeframe		+/- 4 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d

4.2.2.2 Additional visits for extension period (52 weeks of treatment)

Visit specification	V7 telephone	V8	V9 telephone	V10	V11 telephone	V12 telephone	V13 EOT
week	24	28	32	36	40	44	52
timeframe	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d

TABLE 2: VISIT SCHEDULE (TV – TELEPHONE VISIT)

4.3 End of the clinical trial

After conclusion of the clinical trial, patient will receive standard medical care as usual for this kind of disease. Interim analyses are not planned.

As for this study the primary objective will be analyzed after LPLV, the end of the study as a whole will be the date when the clean database is available.

4.4 Justification of trial design

For study objectives, see section 2. For selection of doses, see section 5.9.

4.5 Selection of trial population

Male and female subjects older than 18 years and suffering from type 2 diabetes and CVD are to be screened for participation in the present study according to the inclusion and exclusion criteria described in section4.11.

An individual subject may only be included once in the study.

4.6 Justification of gender distribution

Male and female subjects will be included in the present study representing the population of patients suffering from type 2 diabetes and CVD without any gender prevalence.

4.7 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of the study medication and / or subjects with conditions which may have an impact on the aims of the study are excluded.

4.8 Withdrawal of trial subjects after trial start

4.8.1 Withdrawal

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

- at their own request; at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result
- if, in the investigator's opinion, continuation of study would bear a potential health risk for the patient
- at the specific request of the sponsor
- in case of violation of in- / exclusion criteria; if the subject develops conditions which would have prevented his/her entry into the study according to the in- / exclusion criteria, she / he must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict with the study objectives
- non-compliance with the study conditions or instructions from the investigator's team
- in case of suspected or verified pregnancy

4.8.2 Dropout patients

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been administered at least one dose of the study medication.

Any subject removed (dropout) from the study will remain under medical supervision until discharge is medically acceptable. In all cases, the reason for withdrawal must be recorded in the

eCRF and in the subject's medical records. The sponsor has to be informed about dropout patients by the investigator.

4.8.3 Screening failures

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before being administered at least one dose of the study medication is regarded a "screening failure".

Details for the premature termination of the study as a whole or components thereof (e.g. centers, treatment arms) are provided in section 4.10.

4.8.4 Replacement

Subjects who prematurely discontinue participation after start of treatment – or subjects with major protocol violations – may be replaced only if recruitment is not completed and the drop out rate exceeds the calculated 25 % drop out patients. A replacement of trial subjects has to be released by the PCI.

4.9 Subject identification

After informed consent procedure every subject is given a unique subject identification number by the site. This screening number is only used during recruitment. All eligible subjects get a randomized patient number that will be given by the sponsor during the randomization procedure. All patients (subjects) receiving treatment are identifiable by their patient number at the site.

4.10 Premature termination of the clinical trial

The sponsor has the right to close this study or, if applicable, individual segments thereof (e.g. treatment arms; dose steps; centers) at any time, which may be due but not limited to the following reasons:

- if risk-benefit ratio becomes unacceptable owing to, for example,
- safety findings from this study (e.g. SAEs, elevated bleedings, elevated complications in the study population)
- results of any interim analysis (not planned yet)
- results of parallel clinical studies
- Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity) provided by the manufacturer.
- if the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

4.10.1 Closure of a trial site

For any of the above closures, the following applies:

- closures should occur only after consultation between sponsor and study center(s)
- all affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law
- all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction
- in case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner

Details for individual subject's withdrawal can be found in section 4.8

4.11 In- and exclusion criteria of the trial

4.11.1 Inclusion criteria

Subjects must fulfill all of the following criteria before inclusion in the study:

- Type 2 diabetes duration between 2 and 20 years
- two or more components of metabolic syndrome:
  - HDL cholesterol < 1.0 mmol/L (in males) or < 1.3 mmol/L (in females)
  - Elevated triglycerides (> 1,7 mmol/L)
  - Elevated blood pressure (>130 mmHg systolic and/or >85 mmHg diastolic or antihypertensive treatment)
  - Elevated waist circumference (>102 cm in males , > 85 cm in females)
- OR at least one of the following
  - carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or
  - left ventricular hypertrophy or
  - increased UACR in the absence of other renal diseases than diabetic nephropathy
- increased hsCRP (> 2 mg/l but < 10 mg/l) at or within 6 months prior to screening and/or increased PAI 1 (> 15 ng/ml)at or within 6 months prior to screening(the historical hsCrP or PAI 1 value can be used only if the patient was in stable conditions regarding the concomitant diseases and statin therapy since the time point of measurement)
- age 40 – 75 years at the first screening visit
- stable treatment with statines (if tolerated)
- the informed consent form must be signed before any study specific tests or procedures are done
- ability to understand and follow study-related instructions

4.11.2 Exclusion criteria

Subjects are to be excluded from the study if they display any of the following criteria before and during the trail:

- major CV event with need for oral anticoagulation or platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry
- sustained uncontrolled hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg
- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- lesion or condition, if considered to be a significant risk for major bleeding, this may include
  - active internal bleeding
  - platelet count < 100.000/µL at the screening visit
  - current or recent gastrointestinal ulceration,
  - presence of malignant neoplasm at high risk of bleeding,
  - recent brain or spinal injury, recent brain, spinal or ophthalmic surgery,
  - recent intracranial haemorrhage,
  - known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low
- molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)
- hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- chronic renal failure with eGFR < 15 ml/min (MDRD formula)
- as with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:
  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - active ulcerative gastrointestinal disease

  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding
- known HIV infection at time of screening
- known hypersensitivity to the active substance or to any of the excipients
- Pregnant or breast-feeding woman and woman without adequate method of contraception.

  (The following contraceptive methods are accepted: oral, dermal or vaginal hormonal contraception, contraceptive plaster, long-acting injectable contraceptives, implants that release progesterone, tubal ligation (female sterilization), intrauterine devices that release hormones (hormone spiral), double barrier methods. This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, and female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus)).

4.11.3 Other criteria

- subject is in custody by order of an authority or a court of law
- exclusion periods from other studies or simultaneous participation in other clinical studies
- previous assignment to treatment during this study
- scheduled (elective) surgery after signing the informed consent form
- close affiliation with the investigator (e.g. a close relative) or persons working at the study site
- subject is an employee of GWT-TUD GmbH or Bayer Vital GmbH
- criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety

4.12 Trial procedure overview

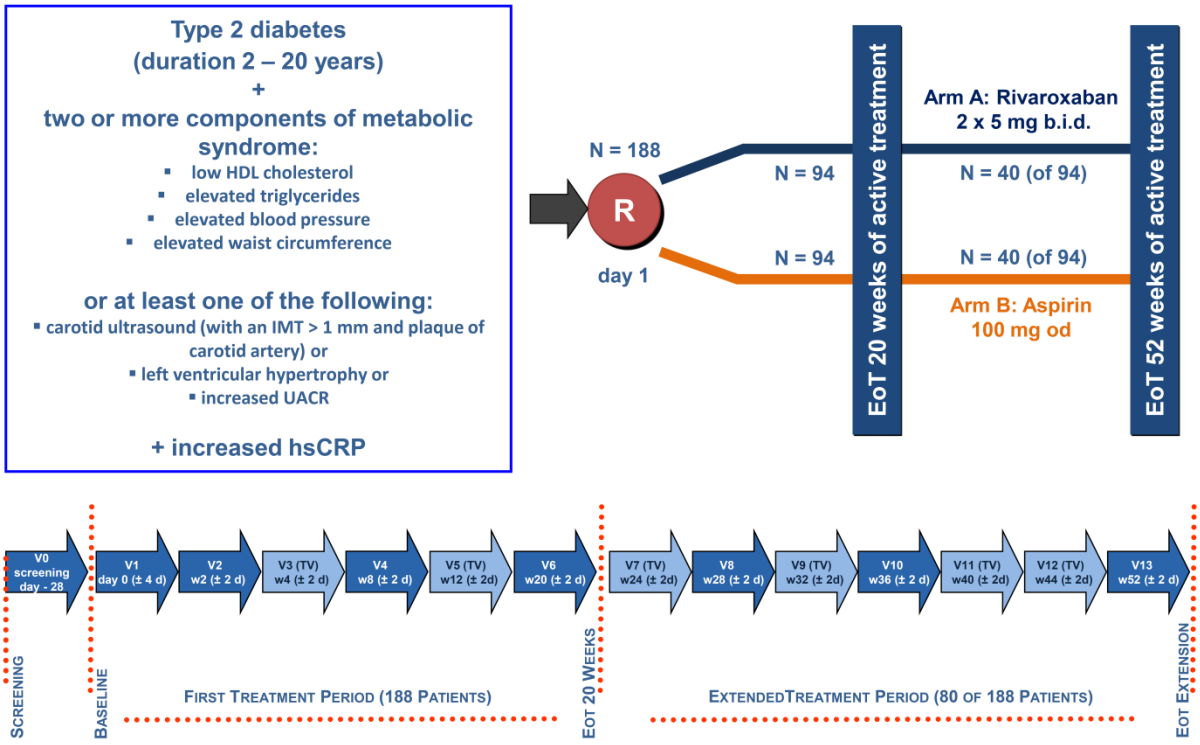


FIGURE 1: TRAIL OVERVIEW (INCLUDING EXTENDED TREATMENT PERIOD)

4.12.1 Tabulated overview

Time deviations from the given time points will be documented as protocol deviations, if applicable. Respective time windows (if any) are specified in the flow chart mentioned.

4.12.2 Description of visits / schedule

VISIT	V0	V1	V2	V3 (TV)	V4	V5 (TV)	V6
WEEK	day -28	day 0 (+/- 4 d)	2 (+/- 2 d)	4 (+/- 2 d)	8 (+/- 2 d)	12 (+/- 2 d)	20 (+/- 2 d)
	SCREEN	BASELINE	TREAT	TREAT	TREAT	TREAT	EOT
STUDY INFORMED CONSENT	✓						✓[A]
SCREENING OF INCLUSION AND EXCLUSION CRITERIA	✓						
VITAL SIGNS (RADIAL PULSE, BLOOD PRESSURE)	✓	✓	✓		✓		✓
RANDOMIZATION*	✓						
BODY HEIGHT	✓						
WAIST/HIP CIRCUMFERENCE BODY WEIGHT	✓						✓
ECG	✓						
MEDICAL HISTORY	✓						
CONCOMITANT MEDICATION/ ACUTE DISEASES	✓	✓	✓	✓	✓	✓	✓
ARTERIAL STIFFNESS		✓					✓
FOREARM BLOOD FLOW		✓					✓
INFLAMMATION LABORATORY(1)		✓					✓
SAFETY LABORATORY(3)	✓	✓	✓		✓		✓
EFFICACY LABORATORY(2)		✓					✓
METABOLIC MARKER(4)		✓					✓
SCREENING LABORATORY(5)	✓						
CARDIOVASCULAR MARKER		✓					✓
LDF INVESTIGATIONS		✓					✓
PLATELET ACTIVATION/ MITOGENIC POTENTIAL		✓					✓
ADVERSE EVENT REPORTING		✓	✓	✓	✓	✓	✓
DISPENSING/RETURN OF MEDICATION/ DRUG ACCOUNTABILITY		✓	✓		✓		✓
PREGNANCY TEST	✓						

TABLE 3: VISIT-SCHEDULE (1 - 54) PARAMETERS TO BE DETERMINED SEE SECTION 4.14; *RANDOMIZATION CAN BE PERFORMED WHEN ALL IN- AND EXCLUSION CRITERIA WERE EXAMINED (RESULTS OF SCREENING LABORATORY MUST BE AVAILABLE). RANDOMIZATION CAN BE PERFORMED BETWEEN BASELINE AND RANDOMIZATION.

[A]: ADDITIONAL INFORMED CONSENT FOR PARTICIPATION TO EXTENDED TREATMENT PERIOD.

4.12.3 Description of visits / schedule of extended treatment period (80 of 188 patients)

VISIT	V7 (TV)	V8	V9 (TV)	V10	V11 (TV)	V12 (TV)	V13
WEEK	24 (+/- 2 d)	28 (+/- 2 d)	32 (+/- 2 d)	36 (+/- 2 d)	40 (+/- 2 d)	44 (+/- 2 d)	52 (+/- 2 d)
	TREAT	TREAT	TREAT	TREAT	TREAT	TREAT	EOT EXTEN-SION
STUDY INFORMED CONSENT FOR EXTENSION PERIOD	✓						
VITAL SIGNS (RADIAL PULSE, BLOOD PRESSURE)		✓		✓			✓
BODY HEIGHT							✓
WAIST/HIP CIRCUMFERENCE BODY WEIGHT							✓
CONCOMITANT MEDICATION/ ACUTE DISEASES	✓	✓	✓	✓	✓	✓	✓
ARTERIAL STIFFNESS							✓
FOREARM BLOOD FLOW							✓
INFLAMMATION LABORATORY(1)							✓
SAFETY LABORATORY(3)		✓		✓			✓
EFFICACY LABORATORY(2)							✓
METABOLIC MARKER(4)							✓
LDF INVESTIGATIONS							✓
ADVERSE EVENT REPORTING	✓	✓	✓	✓	✓	✓	✓
DISPENSING/RETURN OF MEDICATION/ DRUG ACCOUNTABILITY		✓		✓			✓

TABLE 4: TABLE 5: VISIT-SCHEDULE OF EXTENDED TREATMENT PERIOD. PARAMETERS TO BE DETERMINED SEE SECTION 4.14;

4.13 Description of treatment

4.13.1 Visit 0 - Screening (day -28)

Due to the fact that not all subjects may fulfill the inclusion/exclusion criteria, a higher number of subjects, than needed to be valid for the evaluation of the study, will be asked to participate in the screening examination.

Screening examinations will only be performed after having received the subject's written informed consent.

within up 28 days prior to the first study drug administration the following measures / actions will be performed:

- check adherence to inclusion / exclusion criteria
- demographic data
- body weight, height, BMI
- check medical history (in- and exclusion-relevant diseases, metabolic syndromes, risks of VTE events and bleedings, etc.)
- questioning for special behavior (e.g. participation in previous clinical studies)
- check previous medication (medication history); all medication used within the last 12 weeks
- measurement of blood pressure, heart rate (after resting for at least 3 min in supine position)
- screening laboratory for check of in- and exclusion criteria containing measurement of HDL, triglycerides, urinary albumin/creatinin ratio and creatinine
- ECG
- local safety laboratory parameter(including measurement of hsCRP or PAI1 for assessment of in- and exclusion criteria, if not available before screening visit according to in- and exclusion criteria)
- urine pregnancy test
- patients are randomized in one of two treatment groups (Arm A or Arm B). Randomization can be performed when all in- and exclusion criteria were examined (Results of screening laboratory must be available). Randomization can be performed between baseline and randomization

4.13.2 Visit 1 –Baseline (day 0 ± 4 d)

The following actions/measures will be performed:

- check adherence to inclusion / exclusion criteria
- questioning for adverse events, suspected or verified pregnancy and concomitant medication

- measurement blood pressure, heart rate (after resting for at least 3 min in supine position)
- measurement of forearm blood flow
- laserdopplerfluxometry (LDF)
- measurement of arterial stiffness
- efficacy laboratory parameter for endothelial function and coagulation
- efficacy laboratory for composite of biomarkers of inflammation
- blood samples for assessment of platelet function / mitogenic potential
- safety laboratory parameter
- assessment of metabolic marker and cardiovascular marker
- dispensing of study drug along with intake prescriptions

4.13.3 Visit 2 and Visit 4 - Treatment phase

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication
- clinical examination for potential bleeding sides
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- return of study medication and drug accountability
- dispense of new study medication
- safety laboratory parameter

4.13.4 Visit 3 and Visit 5 - Treatment phase (telephone visits)

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication

4.13.5 Visit 6 - End of treatment visit (end of study visit)

The following actions/measures will be performed for patients of Arm A and Arm B:

- questioning for adverse events and concomitant medication
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- measurement of forearm blood flow
- laserdopplerfluxometry (LDF)
- measurement of arterial stiffness

- efficacy laboratory parameter for endothelial function and coagulation:
- efficacy laboratory for composite of biomarkers of inflammation
- blood samples for assessment of platelet function / mitogenic potential
- safety laboratory parameter
- assessment of metabolic marker and cardiovascular marker
- return of study drug / drug accountability and drug dispense in the case of additional treatment period
- advice patient for further treatment after end of study

4.14 Description of additional extension treatment period (80 of 188 patients)

4.14.1 Visit 7, Visit 9, Visit 11 and Visit 12 – Extended treatment phase (telephone visits)

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication

4.14.2 Visit 8 and Visit 10 – Extended treatment phase on site visit

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication
- clinical examination for potential bleeding sides
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- return of study medication and drug accountability
- dispense of new study medication
- safety laboratory parameter

4.14.3 Visit EoT of extended treatment period (end of study visit)

The following actions/measures will be performed for patients of Arm A and Arm B:

- questioning for adverse events and concomitant medication
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- measurement of forearm blood flow
- laserdopplerfluxometry (LDF)
- measurement of arterial stiffness

- efficacy laboratory parameter for endothelial function and coagulation:
- efficacy laboratory for composite of biomarkers of inflammation
- safety laboratory parameter
- assessment of metabolic marker
- return of study drug / drug accountability
- advice patient for further treatment after end of study

4.15 Evaluation of laboratory parameters

Laboratory parameters are centrally or locally determined for the study. During the visits following parameters are determined:

screening laboratory

hemoglobin, hematocrit, ALAT, ASAT, creatinine (PAP method), blood cell count (leucocytes, erythrocytes, platelets), total bilirubin, sodium, potassium, eGFR, HDL-C, triglycerides, cholesterine, urinary albumin/creatinin ratio, creatinine urine, hsCRP (if not available before screening visit according to in- and exclusion criteria), PAI1 (optional), urine pregnancy test

safety laboratory contains:

hemoglobin, hematocrit, ALAT, ASAT, creatinine (PAP method), blood cell count (leucocytes, erythrocytes, platelets), total bilirubin, sodium, potassium, eGFR

inflammation laboratory:

hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, fibrinogen

efficacy laboratory for endothelial function and coagulation:

VCAM-1, ICAM-1, E-Selectin, P-Selectin, CD40L, von Willebrand factor, ADMA, nitrotyrosin, urinary albumin/creatinin ratio, eGFR, UACR, creatinin (serum), fibrinogen (immunolog), prothrombin fragment 1 and 2, TAT, D-Dimer, (protein C, protein S), Quick, aPTT

metabolic marker:

HbA1c, triglycerides, LDL-C, HDL-C, cholesterine

cardiovascular marker:

NT-proBNP, hs-Tnl, GDF-15, MR-ANP

Platelet function / mitogenic potential:

see 4.14.3

4.15.1 Local laboratory:

Safety parameters and parameters that are needed for verification of in- and exclusion criteria are determined by the local laboratory of each study site.

4.15.2 Central laboratory:

All specimen for central evaluation must be sent to:

Labor Studienzentrum Professor Hanefeld
GWT-TUD GmbH
Fiedlerstr. 43,
01307 Dresden
Tel: +49 (0)351 4400 5970
Fax: +49 (0)351 4400 581

Inflammation, efficacy and metabolic parameters are determined in different central laboratories.

responsible laboratory	parameters to be determined
Labor Studienzentrum Professor Hanefeld GWT-TUD GmbH Fiedlerstr. 34, 01307 Dresden / Germany Phone: +49 (0)351 4400 5970 Fax: +49 (0)351 4400 581	HbA1c, hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, eGFR, urinary albumin/creatinin ratio, LDL-C, HDL-C, trigylceride, cholesterine Crea (PAP methode), UACR, VCAM-1, ICAM-1, E-Selectin, P-Selectin, ADMA, Nitrotyrosin, CD40L
Universitätsklinikum Dresden Institut für klinische Chemie und Laboratoriumsmedizin Fetscherstr. 74 01307 Dresden / Germany Phone: +49(0) 351 458 2109 Fax: +49(0) 351 458 4332	Prothrombin fragment 1 and 2; TAT, Protein C, Protein S, D-Dimer, Fibrinogen immunolog., von Willebrand factor; Quick, aPTT
Universitäres Herzzentrum Hamburg Biomarker Labor (AG Zeller) Gebäude O48/4. OG Martinistrasse 52	NT-proBNP, hs-Tnl, GDF-15, MR-ANP

20246 Hamburg / Germany
Phone: +49(0) 40 7410 56575
Fax: +49 (0) 40 7410 40194

Universitätsklinikum Dresden Medizinische Klinik III Fetscherstr. 74 01307 Dresden / Germany Phone: +49(0) 351 458 4233 Fax: +49(0) 351 458 5333	Assessment of platelet activation and mitogenic potential

Further details of handling of specimen and shipment will be specified in the laboratory manual.

4.15.3 Assessment of platelet activation and mitogenic potential

Platelet activation will be assessed by measuring platelet derived microparticles (PMP).Therefore blood will be carefully drawn into CTAD tubes and platelet poor plasma will be obtained after two centrifugations at 2.500 g for 15 minutes. Platelet rich plasma will be prepared by centrifugation for 20 minutes at 800 g. After transfer of the platelet fraction HEP buffer and the phosphodiesterase inhibitor 3-isobutyl-1- methylxanthine (IMBX) will be added to prevent platelet activation and cGMP degradation respectively. Platelet poor and platelet rich plasma will be stored at -80°C until further processing. Subsequently, analysis of platelet microparticles and their mitogenic potential will be performed after sample thawing. PMP will be measured after staining with anti-GP1b antibodies by fluorescence-activated cell sorting (FACS). In addition, magnetic beads linked with anti-GP1 b antibodies will be used to extract PMP from platelet poor plasma. Therefore, samples will be passed through MACs MS separation columns in order to separate platelet-derived microparticles from plasma that contains inhibitors to clotting enzymes. Extracted PMP will then be added to human vascular endothelial cells (HUVECS) and migration (Boyden chamber) as well as proliferation (BrdU) of HUVECs will be assessed with and without PMP with samples from patients undergoing platelet inhibition or rivaroxaban treatment. Platelet rich plasma will be used to measure platelet activation. Therefore, cGMP dependent phosphorylation of vasodilator-stimulated phosphoprotein (VASP) at Ser-157 will be assessed adding a specific AB against VASP-P157 coupled to magnetic beads which will be detected by flow cytometry.

4.16 Duration of the clinical trial in the individual subject

The total duration of the study will be approximately 20 weeks per subject. Subjects are obliged to come to the study center for 5 visits and receive two telephone contacts (visit 3 and visit 5).

4.17 Analyses and reporting

Data will be analyzed and reported after the last subject has been followed the EOT visit.

5 IMP

5.1 Treatments to be given

Treatment Arm	No. of patients	Type of therapy	Treatment	Dose / route	Frequency
A Treatment Group	94	Rivaroxaban	active	5 mg oral (2 x 2.5 mg)	b.i.d.
B Control group	94	Aspirin	comparator	100 mg oral	q.d.

TABLE 6: TREATMENT SCHEDULE

5.2 Description of the IMP – Rivaroxaban (treatment group)

Trade name:	Xarelto®
INN (International Nonproprietary Name)	Rivaroxaban
Galenical form / formulation	film coated tablet (light yellow, round biconvex tablets marked with BAYER-cross)
Strength	2.5 mg (total daily dose of 10 mg)
Further contents	Lactose monohydrate
Type of packaging and content	aluminium foil blisters in cartons of 56 tablets
Manufacturer	Bayer Pharma AG
Marketing authorization holder	Bayer Pharma AG

TABLE 7: IDENTIFICATION OF THE IMP RIVAROXABAN

The indication and contraindications are listed for the strength of 2.5 mg. For dosage 5 mg b.i.d. of Rivaroxaban it is necessary to administer the authorized strength of 2.5 mg twice at intervals of 12 h. Daily, a total of 4 tablets of 2.5 mg strength are taken.

5.2.1 Therapeutic indication of 2.5 mg Rivaroxaban:

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

5.2.2 Contraindications for 2.5 mg Rivaroxaban:

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- lesion or condition, if considered to be a significant risk for major bleeding, this may include
  - current or recent gastrointestinal ulceration,
  - presence of malignant neoplasm at high risk of bleeding,
  - recent brain or spinal injury, recent brain, spinal or ophthalmic surgery,
  - recent intracranial haemorrhage,
  - known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)
- hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- chronic renal failure with eGFR < 15 ml/min (MDRD formula)
- as with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:
  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - active ulcerative gastrointestinal disease
  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding
- pregnancy and breast feeding

5.3 Description of the IMP – Aspirin (ASS 100) (control group)

The IMP ASS 100 TAH of the control group will be preferably used from ratiopharm GmbH. If it becomes necessary (from indefinable reasons), instead of ratiopharm, Aspirin® Bayer or ASS 100 mg of HEXAL can be used as a control IMP in the same dosage. Both medications have an identical authorization profile.

Trade name:	ASS-ratiopharm® 100 mg TAH
INN (International Nonproprietary Name)	acetylsalicylic acid
Galenical form / formulation	film coated tablet (white, round table with one-sided cross)
Strength	100 mg
Further contents	cellulose
Type of packaging and content	cartons of 50 tablets
Manufacturer	ratiopharm GmbH
Marketing authorization holder	ratiopharm GmbH

TABLE 8: IDENTIFICATION OF THE IMP ASPIRIN

For dosage 100 mg of aspirin it is necessary to administer one tablet once a day at intervals of 24 h.

5.3.1 Indication:

Aspirin 100 mg is indicated for

- Angina pectoris
- acute coronary syndrome
- acute myocardial infarction
- prophylaxis of reinfarction after vascular surgery or PCI
- prophylaxis of stroke or TIA after the occurrence of prior events

5.3.2 Contraindications of ASS 100 mg:

Aspirin 100 mg is contraindicated for

- hypersensitivity to the active substance or to any of the excipients
- prior asthmatic episodes in response to salicylates
- gastrointestinal bleeding in medical history, caused by nonsteroidal antiinflammatory drugs
- current or recent gastrointestinal ulceration, with documented bleeding
- increased predisposition to bleeding
- liver or kidney failure
- severe congestive heart failure
- combination with methotrexate ≥ 15 mg per week
- during the last trimester of pregnancy

5.4 Central pharmacy

The IMP are labelled and shipped to the sites on behalf of the sponsor by the central pharmacy in Dresden. The order of the IMP will be in the responsibility of the sponsor. For queries concerning the IMP use following contact:

Klinik-Apotheke
Universitätsklinikum Carl Gustav Carus / TU Dresden
Tel. +49 (0)351 458-19331
Fax +49 (0)351 458-6385

5.5 Labeling of the IMP

The IMP will be used in its commercially available form. Special labeling for the present study is not necessary according to GCP-V §5 (8) as treatment is unblinded. However, to avoid unauthorized usage the package (primary and secondary packaging) will be marked as containing study medication according to GCP by central pharmacy.

A complete record of batch numbers and expiry dates of all study treatment will be maintained in the ISF. Batch numbers of administered IMP will be recorded in the drug accountability log for each individual patient. All study medication used during the trial will be stored at the study site under controlled conditions (protected from light, at room temperature not exceeding 25°C for aspirin) and will be inaccessible to unauthorized personnel. In case the IMP is expired or stored outside the required temperature limits, the respective batch is not to be used anymore for study purposes and has to be put in quarantine until return.

5.6 Drug logistics and accountability

All study drugs will be stored at the study site in accordance with GCP requirements and the instructions given on the package insert and will be inaccessible to unauthorized personnel. Storage conditions and a complete record of batch numbers and expiry dates can be found in the TMF; the site-relevant elements of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drug in writing and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

5.7 Dispensing of IMP

All packages should be inspected visually before distribution to the study subjects. The IMP will be dispensed to the subjects during the following visits by the site personnel. Each subject will get the following amounts of the randomized IMPs.

Visit Week	**V0 day28**	**V1 day 0** ±4d	**V2 2** ±2d	**V3(TV) 4** ±2d	**V4 8** ±2d	**V5(TV) 12** ±2d	**V6 20** ±2d	**Dispensed medication**
Rivaroxaban	-	90 Tabl. (3 Packs)	210 Tabl. (7 Packs)	-	330 Tabl. (11 Packs)	-	*270 Tabl. (9 Packs)*	630 *(+270)* Tabl. = 21 *(+9)* Packs
Aspirin	-	50 Tabl. (1 Pack)	50 Tabl. (1 Pack)	-	50 Tabl. (1 Pack)	-	*100 Tabl. (2 Packs)*	150 *(+100)* Tabl. = 3 *(+2)* Packs

TABLE 9: DRUG DISPENSE FOR FIRST TREATMENT PERIOD (1 PACK RIVAROXABAN CONTAINING 30 TABLETS; 1 PACK ASPIRIN CONTAINING 50 TABLETS);
OPTIONAL: DISPENSE OF IMP AT V6 FOR PATIENTS PARTICIPATIONS TO EXTENDED TREATMENT PERIOD

Visit Week	**V7 (TV) 24**±2d	**V8 28** ±2d	**V9 (TV) 32** ±2d	**V10 36** ±2d	**V11 (TV) 40** ±2d	**V12 (TV) 44** ±2d	**V13 52** ±2d	**Dispensed medication**
Rivaroxaban	-	210 Tabl. (7 Packs)	-	510 Tabl. (17 Packs)	-	-	-	720 Tabl. = 24 Packs
Aspirin	-	50 Tabl. (1 Pack)	-	150 Tabl. (3 Packs)	-	-	-	200 Tabl. = 4 Packs

TABLE 10: DRUG DISPENSE FOR EXTENDED TREATMENT PERIOD (80 OF 188 PATIENTS) (1 PACK RIVAROXABAN CONTAINING 30 TABLETS; 1 PACK ASPIRIN CONTAINING 50 TABLETS)

The dispensing of IMP will be recorded in the drug accountability log in the ISF according to provided templates.

Study subject will receive a medication diary for documentation of intake.

5.8 Assignment of trial subjects to treatment groups

All eligible patients will be randomized at baseline visit V1 (after necessary laboratory parameters are available) using a central block randomization process based at the sponsor's site. The study site requesting randomization of a patient will send a form containing site ID and screening number to the sponsor (Dept. of Medical Consulting; fax **+49 351 25933 198,** in the time frame Monday to Friday 8.00 am to 4.00 pm, not on legal holidays). In return, the site will receive a randomization form containing the randomization number and allocation to treatment arm by fax or email within 30 min.

5.9 Selection of dosage of IMP and frequency of treatment

Rivaroxaban will be administered at a dose of 5 mg (2 x 2.5 mg) twice daily (each 12 h), aspirin will be administered at a dose of 100 mg once daily (each 24 h).

The first dose of either study drug will be administered to the participants at the day of randomisation (visit 1). Further administrations take place at Visit 2 (after 2 weeks) and visit 4 (after 8 weeks).

Rivaroxaban will be administered according to the described instructions. Dosage and frequency of aspirin treatment applied in this study will follow the general specifications of the given SmPC.

For patients participating in the extended treatment period, drug dispense will additionally take place at visit V6 (after 20 weeks), at visit V8 after 28 weeks and at visit V10 after 36 weeks.

5.10 Blinding

Not applicable, open-label study.

5.11 Previous and concomitant medication

Rivaroxaban should not be administered concurrently with CYP3A4 and P-gp inhibitors. Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $CR_{max}R$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp.

Patients who will need the above mentioned therapies are excluded from the study participation.

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors since these drugs generally increase bleeding risk. Patients who need chronic treatment with NSAID or ASA > 100 mg / day or other platelet aggregation inhibitors are excluded from the study participation.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor-Xa tests.

5.11.1 Dosing recommendations before and after invasive procedures, surgical intervention and rescue therapy for clinical emergencies:

If an invasive procedure or surgical intervention is required, Rivaroxaban should be stopped at least 12 hours before the intervention, if possible and based on the clinical judgement of the physician. If a patient is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

The estimated half life of rivaroxaban is 7 to 11 hours; for aspirin irreversible inhibits platelet aggregation.

Both substances have a wide therapeutic window. Therefore, in case of asymptomatic overdosing without overt bleeding complications no specific treatment actions need to be taken and patient should be kept under surveillance. For rivaroxaban, gastrointestinal uptake can be reduced by activated carbon application within 3 h after intake of rivaroxaban, the same is applicable for aspirin. Aspirin might be removed from the circulation by hemodialysis. No specific antidot is available for either drug. In case of bleeding complications study treatment should be interrupted and symptomatic therapy (fluid resuscitation and blood transfusion as well as mechanical measures to control bleeding) should be initiated immediately. In the case of aspirin further bleeding can be prevented by platelet transfusion. In the case of rivaroxaban therapy with prothrombin complex or recombinant factor VIIa should be considered.

5.12 Post-study therapy

After ending of the clinical trial, patients will receive further standard medical care as usual for this kind of disease.

6 Efficacy and safety variables

Specific time points for evaluation of efficacy variables and safety measures are given in 4.13.

6.1 Measurement target variables

6.1.1 Primary target variable

- change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at week 20

Additional primary variable for extension period:

- pulse wave velocity at EOT after 52 weeks

6.1.2 Secondary target variables

- change of area under the FBF curve over 10 cycles of venous congestion (compared to baseline/day 0) at week 20 and EOT Extension
- maximal postischemic skin blood flow (arbitrary units) during reactive hyperaemia after 5 min of forearm ischemia at week 20 and EOT Extension using LDF
- change of postischemic skin blood flow using LDF (compared to baseline/day 0) at week 20 and EOT Extension
- pulse wave velocity at 20 weeks and EoT Extension compared to baseline
- laboratory parameter (see above) at week 20 and EOT Extension

Additional secondary variable for extension period:

- change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at EOT after 52 weeks (EOT Extension)

6.1.3 Measurement of safety analysis

- major bleeding defined as clinically overt and associated with one of the following:
  - decrease in hemoglobin level of 2 g/l or required transfusion of at least 2 units of red cells or
  - involved a critical organ or
  - was fatal, in accordance with the recommendation of the International Society on Thrombosis and Haemostasis (ISTH).
- clinically relevant non-major bleeding defined at least one of the following signs:
  - spontaneous skin hematoma of at least 25 cm

- spontaneous nose bleeding of more than 5 min duration
- macroscopic hematuria, either spontaneous or, if associated with an intervention, lasting more than 24 h
- spontaneous rectal bleeding (more than spotting on toilet paper)
- gingival bleeding for more than 5 min
- bleeding leading to hospitalization and/or requiring surgical treatment
- bleeding leading to a transfusion of less than 2 units of whole blood or red cells
- any other bleeding event considered clinically relevant by the investigator

6.1.4 Rationale for assessment procedures

All parameters evaluated in this study as well as the methods to measure them, are standard variables / methods in clinical practice or non-invasive techniques. They are widely used and generally recognized as reliable, accurate and relevant.

6.2 Applied measurement procedures

6.2.1 Venous occlusion plethysmography for assessment of forearm blood flow FBF:

Endothelium dependent vasodilation of resistance vessels will be assessed in both arms simultaneously using strain-gauge venous occlusion plethysmography (Gutmann Medizinelektronik, Eurasburg, Germany or Hokanson Pletysmograph EC6). Patient rest for at least 20 min in supine position in a temperature controlled room. At both upper arms a cuff for venous occlusion will be placed. On the forearm, at the side of its maximal circumference an elastic strain-gauge is used to assess changes of the forearm circumference after release of the upper arm cuff. At start of each assessment of postischemic vasodilation the upper arm cuff will be inflated to 20 Torr above the arterial blood pressure (but at least 200 Torr) for 5 min to induce forearm ischemia. Thereafter the upper arm cuff will be released for free arterial blood inflow into the forearm. Every 10 sec the upper arm cuff inflates automatically to 40 Torr to induce venous congestion for about 10 sec. These sequences will be repeated 10 times. During venous congestion the arterial blood inflow into the forearm causes an increase of its circumference which depends on the amount of blood inflow. The latter one is determined by forearm vascular resistance due to the arteriolar tense.

6.2.2 Laser Doppler Fluxometry:

The technique of micro-lightguide spectrophotometry and laserdopplerfluxometry (LDF) will be used to measure microvascular skin blood flow and postcapillary tissue oxygenation (sO2) at the lower forearm. LDF skin probes will be placed at the lower forearm and on the thenar surface of the left hand in between the phalanx of the thumb and the metatarsale of Dig II, directly adjacent to the muscle abductor pollicis. Microvascular blood flow and post-capillary sO2 will be measured

in parallel in a tissue depth of 2 mm and 8 mm. Via a cuff on the upper arm a supra-systolic occlusion will be induced for 4 minutes, and thereafter, the postischaemic microvascular blood flow and sO2 will be recorded as a measure of microvascular endothelial function in the skin.
Pulse wave velocity and arterial stiffness:

Measurements will be performed using the Mobil-O-Graph device (IEM Inc., Stolberg, Germany). This device allows the non-invasive oscillometric analysis of blood pressure and pulse wave over 24 hours. Based on pulse wave analysis we calculate the aortic augmentation index as marker of arterial stiffness and pulse wave velocity. The Mobil-O-Graph device has been validated against gold standard procedures such as applanation tonometry (SphygmoCor, AtCor Inc.) and is used in clinical routine.

6.2.3 Pulse wave velocity and arterial stiffness:

Measurements will be performed using the Mobil-O-Graph device (IEM Inc., Stolberg, Germany). This device allows the non-invasive oscillometric analysis of blood pressure and pulse wave over 24 hours. Based on pulse wave analysis we calculate the aortic augmentation index as marker of arterial stiffness and pulse wave velocity. The Mobil-O-Graph device has been validated against gold standard procedures such as applanation tonometry (SphygmoCor, AtCor Inc.).

Each investigator will receive a user manual for the correct application of the techniques.

7 Administrative aspects

7.1 Data documentation

7.1.1 eCRF

All data relevant to this trial are to be documented by the responsible investigator in a web-based eCRF immediately after measurement has been taken. Entering data may be delegated to members of the trial team but the investigator will have to check and sign the eCRF entries. Serious Adverse Event Forms have also to be signed and dated by the investigator.

7.1.2 Source data documentation

Original records, source data, printouts from medical devices, randomization fax etc. will be documented in a separate patient file respectively in a special study file.

All relevant source data should be maintained in this file. The study file should contain:

- signed ICF (informed consent form)
- source data for medical history and previous medication

- checks of in- and exclusion criteria
- randomization form
- source data of:
  - laboratory data (for safety, efficacy parameter)
  - measurements of FBF, LDF, arterial stiffness
  - ECG forms
  - data of physical examinations
- AE /SAE
- visit specific information (what was done at each visit)
- notifications of drug dispense and return

All source data and data identifiable as source data must be signed by the investigator. All study files must contain the patient number (randomization number) for identification and must contain information when and by whom the patient was informed.

If it is necessary to make corrections to any written source data, a single line should be drawn through the original entry, the new entry written in, and the form initialed and dated by the individual making the correction.

mistake		correction
Birth date:	09.10.2014	Birth date: ~~09.10.2014~~09.10.1958 (corr.: initials/date)

7.2 Data management

The IT infrastructure and data management staff will be supplied by GWT. The trial database will be developed and validated prior to data entry based on standard operating procedures at GWT. The data management system is based on commercial trial software (Macro 4.0) and stores the data in a database, storing all changes in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. A regularly backup of all trial data will be performed by InferMed (London). After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

Trial sites will enter data online via Internet. Plausibility checks are run during data entry, thereby detecting discrepancies immediately. The GWT Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via trial software. Discrepancies and implausible values will be clarified in writing between the data manager and the trial site. These electronic queries have to be answered by the trial site without unreasonable delay.

Further details will be specified in the data management manual.

7.3 Data quality

7.3.1 Monitoring

The trial site will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

All investigators agree that the monitor will regularly visit each trial site and assure that the monitor will receive appropriate support in his activities at the trial site, as agreed in separate contracts with each site. The declaration of informed consent includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the eCRFs with the trial subject's medical records (physicians notes, laboratory printouts etc.). The investigator will ensure access for the monitor to all necessary documentation for trial-related monitoring. The purposes of the monitor visits are as follows:

- check the informed consent
- check inclusion and exclusion criteria
- monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs)
- check the completeness and accuracy of entries on the eCRFs
- validate the entries on the eCRFs against those in the source documents (source data verification)
- perform drug accountability checks
- evaluate the progress of the trial
- evaluate compliance with the trial protocol
- assess whether the trial is being performed according to GCP at the trial site
- discuss with the investigator aspects of trial conduct and any deficiencies found.

Monitoring at each trial site will be done for 100 % for the ISF, the patient's informed consent, all in- and exclusion criteria, safety parameters and the drug accountability.

Source data, pre-exisiting disease as well as concomitant medications and disease will be monitored for 50 % of the patient data.Monitoring will be adapted to the quality of data recorded by the trial site. Monitoring activities will also be adapted to pre-visit checks of the data entered to the eCRF or by telephone visits.

A monitoring visit report will be prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation). A follow-up letter will be prepared for the trial site after each visit.

Further details will be given in the Monitoring Manual.

7.3.2 Data quality assurance

The responsibilities of the German Investigators are set out in the German drug law (AMG), GCP-Verordnung (GCP-V), the ICH guideline for Good Clinical Practice (ICH-GCP) and in the Directive 2001/20/EC of the European Union.

7.3.3 Audits/Inspections

As part of quality assurance, the sponsor has the right to audit the trial site and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

In addition, inspections by regulatory health authority representatives and IEC are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

All persons conducting audits will keep all trial subject data and other trial data confidential.

7.3.4 Archiving

All study relevant data, informed consent forms and other important trial materials will be archived for at least 10 years in accordance with §13 Sec. 10 of the national GCP Regulations.

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The ISF is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study center.

8 Ethical and regulatory aspects

8.1 Independent ethics committee

The protocol, ICF and any other supporting study documents will be reviewed by the independent ethics committee (IEC) of the State Chamber of Physicians of Saxony (*Sächsische Landesärztekammer*) prior to study initiation as the leading IRB. Each study site may not begin the study until the responsible authority/committee for that site has given its written approval, signed by the authority chairperson or authorized personnel, and a copy of the approval letter and the approved ICF for that site has been provided to the Investigator.

8.2 Notification of the authorities, approval and registration

Before the start of the clinical trial, all necessary documentation will be submitted to the competent supreme federal authority for approval (Bundesinstitut für Arzneimittel und Medizinprdukte, [BfARM]).

The state authorities in each federal state in which the trial will be conducted will also be notified.

Prior to start of the study, it will be registered under www.clinicaltrials.gov.

8.3 Ethical basis for the clinical trial

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained. The responsible unit (e.g. EC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol

amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

All investigators and other staff involved in the study will be informed that the competent federal authorities and authorized representatives of the sponsor have the right to review trial documentation and the trial subjects' medical records at any time.

Details on discontinuation of the entire study or parts thereof can be found in Section 4.10.

8.4 Obtaining informed consent from trial subjects

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form (ICF) provided by the sponsor. A sample subject information and ICF is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to her/his entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms). The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may she/he enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The ICF will be signed in duplicate, one copy remains with the subject and the second original is to remain in the ISF or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form.

The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm her/his participation in the study by signing each revised informed consent form. Any revised written ICF and written information must receive the IEC / IRB`s approval / favorable opinion in advance of use.

Part of the monitoring activities are to check that the most recent ICF was used before the trial subject was enrolled and that it was dated and signed by the trial subject himself or herself.

8.5 Compensation for health damage of subjects / insurance

All subjects enrolled in this trial are insured in accordance with § 40 AMG article 1 (8) and article 3 under the group insurance contract of GMIHO mbH as a subsidiary company of the sponsor GWT-TUD GmbH with ALLIANZ Versicherungs-AG covering eventually occurring damage caused by the treatment or any actions taken according to the treatment plan. The headquarters, policy number and contact information will be provided in the patient information sheet.

ALLIANZ Versicherungs-AG
10900 Berlin
Fax: 0800 - 4400101

Policy Number: AS-9100294133

8.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects to be identified in the ISF.

9 Statistical methods and sample size calculation

9.1 General statistical considerations

9.1.1 Description of trial subject groups

Patients with type 2 diabetes duration between 2 and 20 years in the age range from 40 – 75 years showing increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml) as well as documented atherosclerotic CVD will be included in this prospective, comparative active controlled, randomized, 2 parallel arms, open study. No further subgroup analyses were intended.

9.1.2 Trial populations

For the analysis, patients not fulfilling the selection criteria of the trial ("non-eligible") will be excluded from the statistical analysis. Only casuistic reports will be provided for this group. All other patients will primarily be evaluated in an intent-to-treat analysis (ITT) (full analysis set, FAS).

Analyses of efficacy endpoints will be performed on the per protocol analysis set (PPS) defined as the subset of subjects of the FAS who have complete data of primary and secondary target variables at the first (V1) and last visit (V6), and who have no major protocol deviations thought to impact on the efficacy conclusions of the trial.

All patients having received at least one application of study medication are generally evaluable for safety and will be included in the safety analysis set (SAS).

9.1.3 Primary target variable

The primary target variable of this study is the change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at week 20 and the difference of PWV between treatment groups at EOT.

9.1.4 Secondary variables

The secondary variables are the change of AUC of forearm blood flow compared to baseline, the maximal postischemic skin blood flow during reactive hyperaemia after 5 min of forearm ischemia, change of postischemic skin blood flow, pulse wave velocity and laboratory parameters.

9.1.5 Interim analysis

An interim analysis is not planned due to the explorative character of the trial.

9.1.6 Missing values and outliers

Missing values will not be imputed. Outliers will be identified by data management and have to be checked by the study physician. According to the decision of data management and study physician, outliers will be kept in the database or set to “missing” or “not available”.

9.1.7 Reporting conventions

P-values ≥ 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “< 0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant digits.

9.1.8 Sample size calculation

The primary variable is change of forearm blood blow with venous occlusion plethysmography(ΔFBF) after forearm ischemia after 20 weeks treatment. The sample size calculation is based on the following assumptions:

$$H0: \Delta FBF_{Riva} \leq \Delta FBF_{ASS}$$

$$H1: \Delta FBF_{Riva} > \Delta FBF_{ASS}$$

- Type I error: $\alpha = 0.05$, one-tailed t-test for independent samples
- Power: 1-ß = 0.90
- Estimated dropout rate : 25 %
- Minimum of expected clinical relevant difference between the groups in changes of maximal forearm blood flow (ΔFBF) = 1.2 ml/100ml with an estimated standard deviation (SD) of σ = 2.4 ml/100ml [Pistrosch, F. et al. Diabetes Care 27: 484-490, 2004]

Sample size should be N = 188 Patients ($N_{1/2}$ = 94 patients per arm) for a valid number of 141 patients for per protocol analysis. This sample size may also provide enough power for further analyses.

Additionally, the second primary variable is difference of PWV between treatment groups at EOT Extension (after 52 week of treatment). The sample size calculation is based on the following assumptions:

$$H0: PWV_{Riva} = PWV_{ASS}$$

$$H1: PWV_{Riva} \neq PWV_{ASS}$$

- Type I error: $\alpha = 0.05$, t-test for independent samples

- Power: 1-ß = 0.80
- Estimated dropout rate : 20 %
- Minimum of expected clinical relevant difference between the groups in PWV = 0.7 m/s with an estimated standard deviation (SD) of σ = 1.0 m/s

Sample size should be N=80 patients (40 patients per arm) for a valid number of 66 patients for per protocol analysis.

In summary the necessary sample size would be N=188 patients for the study up to week 20 including 80 patients for the extension up to week 52.

9.2 Statistical methods

Descriptive or summary statistics will be displayed for continuous data and for categorical data. All continuous variables will be summarised using the following statistics: n (non-missing sample size), mean, 95 % confidence interval, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by subject and visit number. All summary tables will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Comparisons will be tested at the 2-sided 5% significance level. For the primary study endpoint, a one-sided significance level of 5% will be assumed.

T-tests for independent samples will be used for single comparisons between treatment arms (like the primary study endpoint). Analyses of the continuous variables over time will be performed as paired t-Test, repeated measures analysis of variance or mixed models. All analyses of categorical measures will be performed using Fisher´s exact test, McNemar's Test or χ^2 test. Previous correlation analyses of outcome variables and possible predictors will provide evidence for inclusion in analysis. In this trial, most relevant time points for analyses of longitudinal data for secondary study endpoints are at baseline (V1) and after end of treatment (V6).

Individual listings of treatment-emergent adverse events will be provided. The incidence of treatment-emergent adverse events, respectively, will be summarized using WHO SOC terms. Analysis of adverse events will be based on the safety analysis set.

10 Safety

10.1 Definitions of adverse events and adverse drug reactions

10.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after randomization /first intake of study medication in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, or laboratory or ECG test results.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

10.1.2 Adverse drug reaction

An adverse drug reaction (ADR) is any noxious and unintended response to an IMP related to any dose with at least a reasonably possible causal relationship with the IMP.

10.1.3 Serious adverse events and serious adverse reactions

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

- results in death
- is life-threatening

The term 'life-threatening' in the definition refers to an event in which the patient 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 hospitalization or prolongation of existing hospitalization

  A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

  - the admission results in a hospital stay of less than 12 hours
  - the admission is pre-planned(i.e. elective or scheduled surgery arranged prior to the start of the study that is written in the patient / study file)
  - the admission is not associated with an AE (e.g. social hospitalization for purposes of respite care)

  However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
- results in persistent or significant disability / incapacity

  Disability means a substantial disruption of a person's ability to conduct normal life's functions.
- is a congenital anomaly / birth defect
- is another medically important serious event as judged by the investigator

If an AE is classified as an SAE, this is documented on a separate SAE sheet in addition to the standard AE documentation.

10.1.1 Unexpected adverse drug reaction

An unexpected ADR is an ADR for which the nature or severity is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the appropriate reference document, i.e. in the SmPC.

10.1.2 Suspected unexpected serious adverse reactions

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

10.2 Documentation and follow-up of adverse events

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed about the responsibilities and actions required when AEs occur. Trial subjects will be

asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the eCRF.

For the procedure of SAE-reporting see section 10.3.

10.2.1 Classifications for adverse event assessment

All AE/SAE will be assessed and documented by the investigator according to the categories detailed below.

SERIOUSNESS

For each AE, the seriousness must be determined according to the criteria given in section 10.2.1

INTENSITY

The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event: mild, moderate, severe.

CAUSAL RELATIONSHIP

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

For the assessment of the causal relationship to medication following points should be considered:

- laboratory test abnormalities which cannot be explained by concurrent disease or other drugs or chemicals
- the response to withdrawal of the drug (dechallenge) and rechallenge information events in a reasonable time sequence to administration of the drug rechallenge

Possible answers for an assessment of relationship are "yes" or "no".

An ADR/SADR is suspected if the causal relationship is assessed as "yes". Events assessed as "no" are not suspected ADRs/SADRs.

10.2.2 Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).Possible answers are "yes" or "no"

ACTION TAKEN WITH STUDY TREATMENT

Any action on study treatment to resolve the AE is to be documented using the following categories: drug withdrawn, drug interrupted, dose reduced, dose not changed, dose increased, not applicable, unknown.

OTHER SPECIFIC TREATMENT(S) OF ADVERSE EVENTS

- None
- Remedial drug therapy
- Other

OUTCOME

The outcome of all events is to be documented as follows: recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, life-threatening, fatal, unknown

10.2.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the subject will be documented. The observation phase for AEs will start with randomization / first intake of study medication and will end in general with the last visit. In case of ongoing AEs after the last follow-up visit – especially when related to treatment with the study medication – the respective AE will be followed until resolution, if possible. The investigator is responsible for the grading of each category mentioned in section 10.2.1.

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to treatment with the study medication.

10.3 Reporting of serious adverse events

10.3.1 Investigator's notification of the sponsor

The definition of SAEs is given in section 10.1. All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the ISF. This information will be updated as needed.

All SAEs occurring during the study (Screening to EOT) defined in Section 10.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsors safety management. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

All SAEs must be sent via Fax or eMail to:

GWT GmbH
Blasewitzer Str. 43
Germany - 01307 Dresden
Fax: 0351 /259 33 199
eMail: safety@gwtonline.de

NOTIFICATION OF THE IECS / IRBS

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the sponsor and / or by the investigator according to all applicable regulations if requested by the sponsor.

NOTIFICATION OF THE AUTHORITIES

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

SPONSOR'S NOTIFICATION OF THE INVESTIGATIONAL SITE

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

NOTIFICATION OF THE MARKETING AUTHORIZATION HOLDER

The sponsor will also inform the marketing authorization holder about all SAEs and all SUSARs including information reported to the competent supreme authority and ethics committee in accordance with contractual agreements.

10.4 Expected adverse events

10.4.1 Adverse events possibly related to the study medication

For this study, the applicable reference document is the most current version of the SmPC. If relevant new safety information is identified, the information will be integrated into an update of the SmPC and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

SUMMARY OF THE SAFETY PROFILE

The majority of adverse reactions reported for Xarelto® 2.5 mg (Rivaroxaban) (respectively 10 mg daily dose) are bleeding complications (gastrointestinal bleeding, etc.).

Less frequently reported, but more serious, adverse reactions include anemia, allergic reaction, dizziness, headache, hematoma, hypotonia which are listed in the table below. The adverse

reactions are listed by system organ class and frequency using the following convention: very common ("1/10), common ("1/100 to < 1/10), uncommon ("1/1.000 to < 1/100), rare ("1/10.000 to < 1/1.000), very rare (< 1/10.000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders	
Common	anemia
Uncommon	thrombocythemia
Immune system disorders	
Uncommon	allergic reaction, allergic dermatitis
Nervous system disorders	
Common	dizziness, headache, syncope
Uncommon	cerebral and intracranial haemorrhage
Eye disorders	
Common	Eye haemorrhage (including conjunctiva haemorrhage)
Cardiac disorders	
Common	tachycardia
Vascular disorders	
Common	hypotension, haematoma
Not known	Pseudoaneurysm formation following percutaneous intervention

Respiratory, thoracic and mediastinal disorders	
common	Epistaxis
uncommon	Haemoptysis
Gastrointestinal disorders	
Common	Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoe, vomiting
Uncommon	Dry mouth
Hepatobiliary disorders	
Uncommon	Hepatic function abnormal
Rare	Jaundice

Skin and subcutaneous tissue disorders	
Common	Pruritus (incl. uncommon cases of generalized pruritus), rash, ecchymosis
Uncommon	Urticaria, cutaneous and subcutaneous haemorrhage
Musculoskeletal and connective tissue disorders	
Common	Pain in extremity
Uncommon	Haemarthrosis
Rare	Muscle haemorrhage
Unknown	Compartment syndrome secondary to a bleeding
Renal and urinary disorders	
Common	Urogenital tract haemorrhage (incl. haematuria and menorrhagia)
Uncommon	Renal impairment (incl. blood creatinine increased, blood urea increased)
Unkown	Renal failure / acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions	
Common	Fever, peripheral oedema, decreased general strength and energy (incd. fatigue and asthenia)
Uncommon	Feeling unwell (incl. malaise), localized oedema
Investigations	
Common	Increase in transaminase
Uncommon	Increased bilirubin, increased blood alkaline phosphatase, increased LDH, increased lipase, increased amylase, increased GGT
Rare	Bilirubin conjugated increased (with or without concomitant increase of ALT
Injury, poisoning and procedural complications	
Common	Postprocedural haemorrhage (incl. postoperative anemia, wound haemorrhage), contusion, wound secretion

TABLE 11: TABULATED LIST OF ADVERSE REACTIONS

10.5 Special safety precautions of Xarelto®

10.5.1 Overdose

Rare cases of overdose up to 600 mg of Xarelto® have been reported without bleeding complications or other adverse reactions. In the case of overdose see section 5.11.1.

10.5.2 Effects on ability to drive and use machines

Xarelto® has a minor influence on the ability to drive and to use machines. Adverse reactions like syncope or dizziness have been reported to be common. Patients experiencing these adverse reactions should not drive or use machines.

10.6 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. In case of a suspected or verified pregnancy the subject should be excluded from further study treatment.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

11 Use of trial findings and publication

11.1 Reports

11.1.1 Periodic information

The investigator of each site will inform the sponsor monthly about the progress of the trial. These reports will include the number of recruited patients and screening failures as well as dropouts.

11.1.2 Annual safety report of trial subjects

Once a year or on demand, the sponsor will supply a report on the safety of trial subjects in accordance with ENTR/CT 3 with all relevant information during the reference period to the competent supreme federal authority and the responsible ethics committee.

The reference period for the annual report on the safety of trial subjects begins with the date of the first approval of the competent supreme federal authority for trials running with same investigational medicinal product by the sponsor. This date is the reference date for the start of the year of the annual safety report. The sponsor will supply the report within 60 days of one year after the reference date (data-lock point).

11.1.3 Final report

The competent authority and ethics committee will be informed within 90 days that the trial has officially ended. In case the trial is prematurely terminated the notification period is reduced to 15 days. Within one year of the completion of the trial, the competent federal authority and the ethics committee will be provided with a summary of the final report on the clinical trial containing the principle results.

11.2 Publication

It is planned to publish the trial results, in mutual agreement with the CPI, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. The trial will also be registered in a public register (www.clinicaltrials.gov) in accordance with the recommendations of the ICMJE.

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

12 Amendments to the trial protocol

12.1 Changes to trial protocol

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the sponsor, sponsor's representative, the CPI and biometrician, and all authors of this trial protocol. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by all authors of the original trial protocol.

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

12.2 Amendment 1

12.2.1 Overview of changes Amendment 1 (Version 2.0)

On request of the national competent authority (BfArM) the procedure for labeling of the IMP was requested (section 5.5) and minor corrections regarding the in- and exclusion criteria (section 4.11) and the evaluation of laboratory parameters (section 4.14).

12.2.1.1 Changes to the protocol text Amendment 1 (Version 2.0)

In this section, all protocol sections affected by Amendment 1 are detailed and sequence of the sections follows the structure of the original protocol (version 1.0 of 10.06.2014).

The amendment comprises changes to the following sections: sections 4.11and 4.14 and 5.5.

12.2.1.1.1 Changes in section 4.11 In- and Exclusion criteria

Original wording, , page 25 Inclusion criteria (section 4.11.1):

- ~~Type 2 diabetes duration between 2 and 20 years~~
- ~~one of the following documented atherosclerotic CVD:~~
  - ~~major cardiovascular event in medical history (myocardial infarction, stroke, peripheral artery disease or invasive vascular procedure (balloon angioplasty or bypass grafting)) or~~
  - ~~coronary angiography showing a coronary artery stenosis of > 50 % or~~
  - ~~carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or~~
  - ~~left ventricular hypertrophy or~~

- ~~macroalbuminuria in the absence of other renal diseases than diabetic nephropathy~~
- ~~increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml)~~
- ~~age 40 – 75 years~~
- ~~the informed consent form must be signed before any study specific tests or procedures are done~~
- ~~confirmation of the subject's health insurance coverage prior to the first screening visit~~
- ~~age at least 18 years (inclusive) at the first screening visit~~
- ~~ability to understand and follow study-related instructions~~

Revised wording, page 25 Inclusion criteria (section 4.11.1):

- Type 2 diabetes duration between 2 and 20 years
- one of the following documented atherosclerotic CVD:
  - major cardiovascular event in medical history (myocardial infarction, stroke, peripheral artery disease or invasive vascular procedure (balloon angioplasty or bypass grafting)) or
  - coronary angiography showing a coronary artery stenosis of > 50 % or
  - carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or
  - left ventricular hypertrophy or
  - macroalbuminuria in the absence of other renal diseases than diabetic nephropathy
- increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml)
- age 40 – 75 years at the first screening visit
- stable treatment with statines (if tolerated)
- the informed consent form must be signed before any study specific tests or procedures are done
- confirmation of the subject's health insurance coverage prior to the first screening visit
- ability to understand and follow study-related instructions

Changes were also made in the synopsis.

Original wording, page 25 Exclusion criteria (section 4.11.2):

- ~~CV event with need for oral anticoagulation or dual platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry~~
- ~~sustained uncontrolled hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg~~
- ~~concomitant conditions and therapies~~
- ~~hypersensitivity to the active substance or to any of the excipients~~
- ~~active clinically significant bleeding~~
- [...]

Revised wording, page 25 Exclusion criteria (section 4.11.2)

- CV event with need for oral anticoagulation or dual platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry
- sustained uncontrolled hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg
- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- [...]

12.2.1.1.2 Changes in section 4.14 Evaluation of laboratory parameters

Original wording, page 31 (section 4.14):

~~**safety laboratory contains:**~~

~~hemoglobin, hematocrit, platelets, ALAT, ASAT, creatinine, GFR (calculated), blood cell count, total bilirubin, sodium, potassium, hsCRP, PAI1, eGFR~~

~~**efficacy laboratory for endothelial function and coagulation:**~~

~~VCAM-1, ICAM-1, E-Selectin, P-Selectin, CD40L, von Willebrand factor, ADMA, nitrotyrosin, microalbuminuria, eGFR, UACR, creatinin (serum), fibrinogen (immunolog), prothrombin fragment 1 and 2, PAP, TAT, D-Dimer, (protein C, protein S)~~

Revised wording, page 31, (section 4.14)

safety laboratory contains:

hemoglobin, hematocrit, platelets, ALAT, ASAT, creatinine, GFR (calculated), blood cell count (leucocytes, erythrocytes), total bilirubin, sodium, potassium, hsCRP, PAI1, eGFR

efficacy laboratory for endothelial function and coagulation:

VCAM-1, ICAM-1, E-Selectin, P-Selectin, CD40L, von Willebrand factor, ADMA, nitrotyrosin, microalbuminuria, eGFR, UACR, creatinin (serum), fibrinogen (immunolog), prothrombin fragment 1 and 2, TAT, D-Dimer, (protein C, protein S)

Original wording, page 37 (section 4.14.2):

~~**responsible laboratory**~~	~~**parameters to be determined**~~
~~Labor Studienzentrum Professor Hanefeld GWT-TUD GmbH Fiedlerstr. 34, 01307 Dresden~~	~~HbA1c, hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, eGFR, Microalbuminuria, LDL-C, HDL-C, trigylceride, Crea (PAPP), HbA1c, UACR~~

~~Tel: +49 (0)351 4400 5970~~
~~Fax: +49 (0)351 4400 581~~

~~Universitätsklinikum Dresden~~ ~~Institut für klinische Chemie und Laboratoriumsmedizin~~ ~~Fetscherstr. 74~~ ~~01307 Dresden~~ ~~Tel: +49(0) 351 458 2109~~ ~~Fax: +49(0) 351 458 4332~~	~~Prothrombin fragment 1, 2; PAP, TAT, Protein C, Protein S, D-Dimer, VCAM-1, ICAM-1, E-Selectin, P-Selectin, Fibrinogen, CD40L, von Willebrand factor, ADMA, Nitrotyrosin~~

Revised wording, page 37, (section 4.14.2)

responsible laboratory	**parameters to be determined**
Labor Studienzentrum Professor Hanefeld GWT-TUD GmbH Fiedlerstr. 34, 01307 Dresden Tel: +49 (0)351 4400 5970 Fax: +49 (0)351 4400 581	HbA1c, hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, eGFR, Microalbuminuria, LDL-C, HDL-C, trigylceride, Crea (PAPP), UACR, ALAT, ASAT
Universitätsklinikum Dresden Institut für klinische Chemie und Laboratoriumsmedizin Fetscherstr. 74 01307 Dresden Tel: +49(0) 351 458 2109 Fax: +49(0) 351 458 4332	Prothrombin fragment 1and 2; TAT, Protein C, Protein S, D-Dimer, VCAM-1, ICAM-1, E-Selectin, P-Selectin, Fibrinogen immunolog., CD40L, von Willebrand factor, ADMA, Nitrotyrosin,

12.2.1.1.3 Changes in section 5.5 Labeling of IMP

Original wording, page 43 (section 5.5):

~~The IMP will be used in its commercially available form. Special labeling for the present study is not necessary according to GCP-V §5 (8) as treatment is unblinded. However, to avoid unauthorized usage the package (cartons) will be marked as containing study medication according to GCP by central pharmacy. […]~~

Revised wording, page 43 (section 5.5):

The IMP will be used in its commercially available form. Special labeling for the present study is not necessary according to GCP-V §5 (8) as treatment is unblinded. However, to avoid unauthorized usage the package (primary and secondary packaging) will be marked as containing study medication according to GCP by central pharmacy. […]

12.3 Amendment 2

12.3.1 Overview of changes Amendment 2 (Version 3.0)

On request of the independent ethics committee (EK) the general aspect of the withdrawal of aspirin before randomization in patients with an indication for taking the medication has been revised (section 4.2.1 and 5.9). Accordingly, the visits (screening visit and baseline visit) have been revised (section 4.12.2 and 5.7).

Due to the comments of the EK the patient population was adjusted to the effect of inclusion of patients with a high cardiovascular risk instead of cardiovascular disease. Please note for general information: in the Protocol, the definition of "cardiovascular disease" was replaced by "high cardiovascular risk". Therefore the inclusion criteria and the major exclusion criterion were adapted and in the inclusion criteria the statement tot he patient's insurance was deleted (section 4.11.1)

Furthermore the process for establishment of a DSMB was adapted (section 3.6).

Section5.2.1wasadjusted according to the approved indication of the IMP Rivaroxaban 2.5 mg.

12.3.1.1 Changes to the protocol text Amendment 2 (Version 3.0)

In this section, all protocol sections affected by Amendment 2 are detailed and sequence of the sections follows the structure of the original protocol (version 2.0 of 08.07.2014).

The amendment comprises changes to the following sections: sections 4.11and 4.14 and 5.5.

12.3.1.1.1 Changes of study title

Original wording, page:

~~Microvascular and antiinflammatory Effects of Rivaroxaban compared to low dose aspirin in type 2 diabetic patients with cardiovascular disease and subclinical inflammation~~

Revised wording, page:

Microvascular and antiinflammatory Effects of Rivaroxaban compared to low dose aspirin in type 2 diabetic patients with very high cardiovascular risk and subclinical inflammation

12.3.1.1.2 Adaption of Risk-Benefit-Assessment

Original wording, page 20 (section 2.5):

[…]

~~However, since all patients have documented CVD and therefore the indication for secondary prevention of cardiovascular damage with aspirin 100 mg as standard care, even the control group (which receives standard treatment) has a slightly increased bleeding risk. To minimize these risks for the patients we will conduct four safety visits during the treatment of 20 weeks of~~

~~study medication and will not include patients with an increased risk of bleeding as stated in the exclusion criteria.~~

~~In conclusion there is clear evidence, that patients with a high cardiovascular risk in a state of secondary prevention need a treatment. The standard treatment today is low dose aspirin, but in our point of view considering the expected advantages of rivaroxaban at a low dose would outweigh the possible increased risk of bleeding.~~

Revised wording, page 20 (section 2.5):

[…]

Since all patients of our planned investigation have a high risk for cardiovascular disease a primary prevention of CV events with aspirin 100 mg is recommended by several guidelines (14) however, this recommendation is not so strong as the indication for aspirin in the case of secondary prevention. In Germany the therapeutic costs for a primary prevention with aspirin 100 mg even in high risk patients are not covered by general health insurance, therefore a lot of patients do not get a prescription of this medication. The inclusion of this patients with a high CV risk but without a major CV event in medical history would offer the possibility to cover high risk patients with a recommended treatment for the duration of the study. To minimize the bleeding risk for the patients we will conduct four safety visits during the treatment of 20 weeks of study medication and will not include patients with an increased risk of bleeding as stated in the exclusion criteria.

In conclusion there is scientific evidence, that patients with a very high cardiovascular risk in a state of primary prevention and with a low risk for bleeding should be treated. The standard recommended treatment today is low dose aspirin, but in our point of view considering the expected advantages of rivaroxaban at a low dose would outweigh the possible increased risk of bleeding.

12.3.1.1.3 Changes in the Inclusion criteria

Original wording, page 27 (section 4.11.1):

- ~~Type 2 diabetes duration between 2 and 20 years~~
- ~~one of the following documented atherosclerotic CVD:~~
  - ~~major cardiovascular event in medical history (myocardial infarction, stroke, peripheral artery disease or invasive vascular procedure (balloon angioplasty or bypass grafting)) or~~
  - ~~coronary angiography showing a coronary artery stenosis of > 50 % or~~
  - ~~carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or~~
  - ~~left ventricular hypertrophy or~~
  - ~~macroalbuminuria in the absence of other renal diseases than diabetic nephropathy~~
- ~~increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml)~~
- ~~age 40 – 75 years at the first screening visit~~

- ~~stable treatment with statines (if tolerated)~~
- ~~the informed consent form must be signed before any study specific tests or procedures are done~~
- ~~cornfirmation od the subject´s health insurance coverage prior to the first screening visit~~
- ~~ability to understand and follow study-related instructions~~

Revised wording, page 27 (section 4.11.1):

- Type 2 diabetes duration between 2 and 20 years
- two or more components of metabolic syndrome:
  - HDL cholesterol < 1.0 mmol/L (in males) or < 1.3 mmol/L (in females)
  - Elevated triglycerides (> 1,7 mmol/L)
  - Elevated blood pressure (>130 mmHg systolic and/or >85 mmHg diastolic or antihypertensive treatment)
  - Elevated waist circumference (>102 cm in males , > 85 cm n females)
- OR at least one of the following
  - carotid ultrasound showing an IMT > 1 mm and plaque of carotid artery or
  - left ventricular hypertrophy or
  - increased UACR in the absence of other renal diseases than diabetic nephropathy
- increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml)
- age 40 – 75 years at the first screening visit
- stable treatment with statines (if tolerated)
- the informed consent form must be signed before any study specific tests or procedures are done
- ability to understand and follow study-related instructions

The changes were made in the same way in the synopsis.

12.3.1.1.4 Changes in the exclusion criteria – section 4.11.2

Original wording, page 28 (section 4.11.2):

- ~~CV event with need for oral anticoagulation or dual platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry~~

[…]

Revised wording, page 28 (section 4.11.2):

- major CV event with need for oral anticoagulation or platelet inhibitor therapy or acute coronary syndrome < 12 month before study entry

[…]

The changes were made in the same way in the synopsis.

12.3.1.1.5 Changes of withdraw of aspirin treatment before randomization (section 4.2.1 and 5.9)-

Original wording, page 23 (section 4.2.1):

[…]

~~Concomitant aspirin treatment for secondary prevention of CVD must be stopped at least 10 days before randomization.~~

[…]

Revised wording, page 23 (section 4.2.1):

Sentence deleted.

Original wording, page 45 (section 5.9):

[…]

~~Rivaroxaban will be administered according to the described instructions. Dosage and frequency of aspirin treatment applied in this study will follow the general specifications of the given SmPC. Subjects who are treated with aspirin for prophylaxis of recurrent cardiovascular event (as indicated see 5.3) must stop this treatment at least 10 days before intake of the study drug.~~

Revised wording, page 45 (section 5.9):

[…]

Sentence deleted.

12.3.1.1.6 Revision of timelines of screening and baseline visit (section 4.12.1 / and 5.7)-

The treatment changes before the randomization (no suspension of ASS therapy) result in an adjustment of the timelines of the screening and baseline visit.

Original wording, page 31 (section 4.12.2):

~~VISIT~~	~~V0~~	~~V1~~	~~V2~~	~~V3 (TV)~~	~~V4~~	~~V5 (TV)~~	~~V6~~
~~WEEK~~	~~-2 (+/- 7 d)~~	~~0~~	~~2 (+/- 2 d)~~	~~4 (+/- 2 d)~~	~~8 (+/- 2 d)~~	~~12 (+/- 2 d)~~	~~20 (+/- 2 d)~~
	~~SCREEN~~	~~BASELINE~~	~~TREAT~~	~~TREAT~~	~~TREAT~~	~~TREAT~~	~~EOT~~

[…]

Revised wording, page 31 (section 4.12.2):

VISIT	V0	V1	V2	V3 (TV)	V4	V5 (TV)	V6
WEEK	day -10	day 0 (+/- 4 d)	2 (+/- 2 d)	4 (+/- 2 d)	8 (+/- 2 d)	12 (+/- 2 d)	20 (+/- 2 d)
	SCREEN	BASELINE	TREAT	TREAT	TREAT	TREAT	EOT

[…]

Original wording, page 44 (section 5.7):

~~Visit~~ Week	~~V0~~ ~~-2~~	~~V1~~ ~~0~~ ±2d	~~V2~~ ~~2~~ ±2d	~~V3 (TV)~~ ~~4~~ ±2d	~~V4~~ ~~8~~ ±2d	~~V5 (TV)~~ ~~12~~ ±2d	~~V6~~ ~~20~~ ±2d	~~Dispensed medication~~
[…]	[…]							
[…]	[…]							

Revised wording, page 44 (section 5.7):

Visit Week	V0 day -10	V1 day 0 ±4d	V2 2 ±2d	V3(TV) 4 ±2d	V4 8 ±2d	V5(TV) 12 ±2d	V6 20 ±2d	Dispensed medication
[…]	[…]							
[…]	[…]							

In section 4.12 / page 4.12Figure 1: Trail overview was adapted accordingly.

12.3.1.1.7 Changes in section 3.6 – Data and Safety Monitoring Board

Original wording, page 21 (section 3.6):

~~A Data and Safety Monitoring Board is deemed not to be necessary for this study as this is a multi-center, open-label study with a low risk for participating subjects, i.e. subjects are expected to experience only minor side effects, and interim analyses are not crucial for the protection of the subjects.~~

Revised wording, page 21 (section 3.6):

A Data Safety Monitoring Board (DSMB) of independent experts will be set up. It will consist of two physicians and one statistician who are not involved in the conduct of the trial. The task of the DSMB is to oversee the safety of the trial subjects in the clinical trial by periodically assessing the safety and efficacy of the trial therapy and to monitor the integrity and validity of the data collected and the conduct of the clinical trial.

Throughout this process of surveillance, the DSMB will provide the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected. The data necessary for the DSMB to fulfill this function will be provided by the sponsor as determined by the DSMB charter.

12.3.1.1.8 Changes in section 5.2.1 – Therapeutic indication of Rivaroxaban 2.5 mg

Original wording, page 40 (section 5.2.1):

~~Prophylaxis of venous thromboembolism in adult patients after hip or knee joint replacement.~~

Revised wording, page 40 (section 5.2.1):

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

12.4 Amendment 3

12.4.1 Overview of changes Amendment 3 (Version 4.0)

The changes in this amendment relate to the specification of laboratory parameters (section 4.14) and are not substantial. These changes do not require the approval of the ethics committee and the competent authority (BfArM) but will be e submitted to the authorities for information.

Section 2 - Objectives of the clinical trial

Original wording, page 19 (section 2.3) and synopsis:

[…]

~~**Secondary objectives**~~

- ~~[….]~~
- ~~VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin~~
- ~~hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes~~
- ~~metabolic marker: fasting plasma glucose, HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C~~

Revised wording, page 19 (section 2.3):

[...]

Secondary objectives

- VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin, P-Selectin, CD40-L
- hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes, MPO, IL-6, IL-8
- metabolic marker: HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C
- coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1 + 2, D-Dimer, Protein C, Protein S, TAT

Section 4 – Trial conduct

Revised and additional wording, page 31 (section 4.12.2):

Addition and definition of screening laboratory and specification of randomization after screening visit.

Inflammation laboratory will be done at baseline visit (V1)

Additional wording, page 33 (section 4.13.1):

[…]

- screening laboratory for check of in- and exclusion criteria containing measurement of HDL, triglycerides, urinary albumin/creatinin ratio and creatinine

Additional wording, page 33 (section 4.13.1):

[…]

- patients are randomized in one of two treatment groups (Arm A or Arm B). Randomization can be performed when all in- and exclusion criteria were examined (Results of screening laboratory must be available). Randomization can be performed between baseline and randomization

Original wording, page 33 (section 4.13.2)

[…]

- check previous medication (medication history); all medication used within the last 12 weeks […]

Revised wording, page 33 (section 4.13.2)- Deletion of this paragraph due to repetition

[…]

- ~~check previous medication (medication history); all medication used within the last 12 weeks […]~~

Section 4.14 - Evaluation of laboratory parameters

Original wording, page 36 (section 4.14) and synopsis:

~~**safety laboratory contains:**~~

~~hemoglobin, hematocrit, platelets, ALAT, ASAT, creatinine, GFR (calculated), blood cell count (leucocytes, erythrocytes), total bilirubin, sodium, potassium, hsCRP, PAI1, eGFR~~

~~INFLAMMATION LABORATORY:~~

~~hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, fibrinogen, leucocytes, platelets~~

[…]

Revised and additional wording, page 36 (section 4.14):

[…]

screening laboratory

hemoglobin, hematocrit, ALAT, ASAT, creatinine (PAP method), blood cell count (leucocytes, erythrocytes, platelets), total bilirubin, sodium, potassium, eGFR, HDL-C, triglycerides, cholesterine, urinary albumin/creatinin ratio, creatinine urine, hsCRP, PAI1 (optional), urine pregnancy test

safety laboratory contains:

hemoglobin, hematocrit, ALAT, ASAT, creatinine (PAP method), blood cell count (leucocytes, erythrocytes, platelets), total bilirubin, sodium, potassium, eGFR

inflammation laboratory:

hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, fibrinogen

efficacy laboratory for endothelial function and coagulation:

VCAM-1, ICAM-1, E-Selectin, P-Selectin, CD40L, von Willebrand factor, ADMA, nitrotyrosin, urinary albumin/creatinin ratio, eGFR, UACR, creatinin (serum), fibrinogen (immunolog), prothrombin fragment 1 and 2, TAT, D-Dimer, (protein C, protein S)

metabolic marker:

HbA1c, triglycerides, LDL-C, HDL-C, cholesterine

Original wording, page 37 (section 4.14.2) and synopsis :

[…]

~~responsible laboratory~~	~~parameters to be determined~~
~~Labor Studienzentrum Professor Hanefeld GWT-TUD GmbH Fiedlerstr. 34, 01307 Dresden Tel: +49 (0)351 4400 5970 Fax: +49 (0)351 4400 581~~	~~HbA1c, hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, eGFR, Microalbuminuria, LDL-C, HDL-C, trigylceride, Crea (PAPP), UACR, ALAT, ASAT~~
~~Universitätsklinikum Dresden Institut für klinische Chemie und Laboratoriumsmedizin Fetscherstr. 74 01307 Dresden Tel: +49(0) 351 458 2109~~	~~Prothrombin fragment 1 and 2; TAT, Protein C, Protein S, D-Dimer, VCAM-1, ICAM-1, E-Selectin, P-Selectin, Fibrinogen immunolog.,~~

~~Fax: +49(0) 351 458 4332~~	~~CD40L, von Willebrand factor, ADMA, Nitrotyrosin~~

[…]

Revised and wording, page 37 (section 4.14.2):

responsible laboratory	**parameters to be determined**
Labor Studienzentrum Professor Hanefeld GWT-TUD GmbH Fiedlerstr. 34, 01307 Dresden Tel: +49 (0)351 4400 5970 Fax: +49 (0)351 4400 581	HbA1c, hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, eGFR, Microalbumine, LDL-C, HDL-C, trigylceride, Crea (PAP methode), UACR, VCAM-1, ICAM-1, E-Selectin, P-Selectin, ADMA, Nitrotyrosin, CD40L
Universitätsklinikum Dresden Institut für klinische Chemie und Laboratoriumsmedizin Fetscherstr. 74 01307 Dresden Tel: +49(0) 351 458 2109 Fax: +49(0) 351 458 4332 […]	Prothrombin fragment 1 and 2; TAT, Protein C, Protein S, D-Dimer, Fibrinogen immunolog., von Willebrand factor

12.5 Amendment 4

12.5.1 Overview of changes Amendment 4 (Version 5.0)

The changes in this amendment relate to the specification of one Inclusion criterion (the timepoint of an increased hsCRP measurement) and the evaluation of additional laboratory parameters (section 4.14) as well as additional central laboratory. Changes of the In- and Exclusion criteria require the approval of the ethics committee and the competent authority (BfArM). The changes in this amendment relate to t. The changes modify one inclusion criterion but are not relevant for safety issues.

Specification of the inclusion criterion: In- and exclusion criteria of the trial (4.11 / 4.11.1)

Original wording Synopsis and chapter 4.11.1

- ~~increased hsCRP (> 2 mg/l but < 10 mg/l) and/or increased PAI 1 (> 15 ng/ml)~~

Revised wording: Synopsis and chapter 4.11.1

- increased hsCRP (> 2 mg/l but < 10 mg/l) at or within 6 months prior to screening and/or increased PAI 1 (> 15 ng/ml)at or within 6 months prior to screening (the historical hsCRP

or PAI 1 value can be used only if the patient was in stable conditions regarding the concomitant diseases and statin therapy since the time point of measurement)

Specification and addition of laboratory

Original wording: Synopsis, Secondary and other objectives (section 2.3),

- ~~coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1+2, D-Dimer, Protein C, Protein S, TAT~~

Additional wording: Synopsis, Secondary and other objectives (2.3)

- coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1+2, D-Dimer, Protein C, Protein S, TAT, Quick, aPTT
- cardiovascular marker: NT-proBNP, hs-Tnl, GDF-15, MR-ANP

Addition of assessment of cardiovascular marker in Visit 1 and Visit 6 (section 4.13.2 and 4.13.5) and addition of Visit schedule (section 4.12.2).

Addition of central laboratory for evaluation of cardiovascular marker (section 4.14.2)

Universitäres Herzzentrum Hamburg — NT-proBNP, hs-Tnl, GDF-15, MR-ANP
Biomarker Labor (AG Zeller)
Gebäude O48/4. OG
Martinistrasse 52
20246 Hamburg / Germany
Phone: +49(0) 40 7410 56575
Fax: +49 (0) 40 7410 40194

Expansion of the screening period to 28 days. Changes were made in the following sections:

Original wording: section 4.2.2, section 4.12.2 and section 4.13.1

~~Visit specification~~	~~V0 screening~~	~~V1 baseline~~	~~V2~~	~~V3 telephone~~	~~V4~~	~~V5 telephone~~	~~V6 EOT~~
~~week~~	~~day -10~~	~~day 0~~	~~2~~	~~4~~	~~8~~	~~12~~	~~20~~
~~timeframe~~		~~+/- 4 d~~	~~+/- 2 d~~	~~+/- 2 d~~	~~+/- 2 d~~	~~+/- 2 d~~	~~+/- 2 d~~

Revised Wording: section 4.2.2, section 4.12.2 and section 4.13.1

Visit specification	**V0 screening**	**V1 baseline**	**V2**	**V3 telephone**	**V4**	**V5 telephone**	**V6 EOT**
week	day -28	day 0	2	4	8	12	20
timeframe		+/- 4 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d

12.7 Amendment 5

12.7.1 Overview of changes Amendment 5 (Version 6.0)

The changes in this amendment relate to the extended trial duration for 80 of 188 patients included into the study. Due to the extension of treatment, a second primary endpoint variable will be included into the protocol.

Changes of the trial duration require the approval of the ethics committee and the competent authority (BfArM). The changes did not modify inclusion or exclusion criteria however, the subject information and informed consent form were affected. The changes are not relevant for safety issues.

Synopsis

Original wording Synopsis Treatment period and Timeplan (4.1)

Treatment period	~~20 weeks~~	
Time plan	~~First patient first visit (FPFV):~~	~~January 2014~~
	~~Last patient first visit (LPFV):~~	~~May 2016~~
	~~Last patient last visit (LPLV):~~	~~February 2017~~
	~~DataBase Lock:~~	~~December 2017~~
	~~Final study report:~~	~~March 2018~~

Revised wording Synopsis Treatment period and Timeplan:

Treatment period	20 weeks + additional 32 weeks (extension study for 80 patients)	
Time plan	First patient first visit (FPFV):	April 2015
	Last patient first visit (LPFV):	July 2017
	Last patient last visit (LPLV):	August 2018
	Database Lock:	December 2018
	Final study report:	April 2019

Original wording Synopsis primary objectives and 2.2:

Study objectives	~~**Primary objectives**~~ ~~Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 20 weeks treatment between rivaroxoban and aspirin therapy~~

Revised wording Synopsis primary objectives and 2.2:

Study objectives	**Primary objectives** Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 20 weeks treatment between rivaroxoban and aspirin therapy Additionally the difference of arterial stiffness after the end of the extension study (week 52) between rivaroxoban and aspirin therapy will be evaluated.

Original wording Synopsis secondary objectives and 2.3:

Study objectives	~~**Secondary objectives**~~ ~~• change of peripheral skin microcirculatory function (measured by laserdopplerfluxmetry; LDF)~~ ~~• LDF baseline~~ ~~• LDF after ischemia (endothelial function)~~ ~~• arterial stiffness measured by Mobilograph (IEM Inc.)~~ ~~• laboratory markers for endothelial function~~ ~~• VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin, P-Selectin, CD40-L~~ ~~• Microalbuminuria, eGFR~~ ~~• composite of biomarkers of inflammation~~ ~~• hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes, MPO, IL-6, IL-8~~ ~~• side effects: major bleeding according to ISTH, symptomatic thromboembolic events~~ ~~• metabolic marker: HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C~~ ~~• coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1+2, D-Dimer, Protein C, Protein S, TAT, Quick, aPTT~~ ~~• cardiovascular marker: NT-proBNP, hs-TnI, GDF-15, MR-ANP~~

Revised wording Synopsis secondary objectives and 2.3:

Study objectives	**Secondary objectives** ▪ change of peripheral skin microcirculatory function (measured by laserdopplerfluxmetry; LDF) after 20 and 52 weeks of treatment ▪ LDF baseline ▪ LDF after ischemia (endothelial function) ▪ arterial stiffness measured by Mobilograph (IEM Inc.) after 20 weeks of tretament ▪ laboratory markers for endothelial function ▪ VCAM, ICAM, E-Selectin, ADMA, Nitrotyrosin, P-Selectin, CD40-L ▪ Microalbuminuria, eGFR ▪ composite of biomarkers of inflammation ▪ hsCRP, PAI-1, MCP-1, MMP-9, fibrinogen, leucocytes, MPO, IL-6, IL-8 ▪ side effects: major bleeding according to ISTH, symptomatic thromboembolic events ▪ metabolic marker: HbA_{1c}, lipids: triglycerides, LDL-C, HDL-C ▪ coagulation: von Willebrand-Factor, Fibrinogen, Prothrombinfragment 1+2, D-Dimer, Protein C, Protein S, TAT, Quick, aPTT ▪ cardiovascular marker: NT-proBNP, hs-TnI, GDF-15, MR-ANP **Additional secondary objective for extension period:** ▪ Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 52 weeks treatment

Original wording Synopsis Study endpoints and 6.1.1 and 6.1.2:

Study end points	**Primary variable** ▪ ~~change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at EOT~~

Study end points	**Secondary variables** ▪ ~~change of the area under the postischemic FBF curve over 10 cycles of intermittent venous congestion (compared to baseline)~~ ▪ ~~maximal postischemic skin blood flow (arbitrary units) during reactive hyperaemia after 5 min of forearm ischemia at EOT using LDF~~ ▪ ~~change of postischemic skin blood flow (compared to baseline) using LDF~~ ▪ ~~Pulse wave velocity at EOT compared to baseline~~ ▪ ~~laboratory parameter (see above) at EOT~~

Revised wording Synopsis Study Endpoints and 6.1.1 and 6.1.2:

Study end points	**Primary variable** ▪ change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at 20 weeks **Additional primary variable for extension period:** ▪ pulse wave velocity at EOT after 52 weeks
Study end points	**Secondary variables** ▪ change of the area under the postischemic FBF curve over 10 cycles of intermittent venous congestion (compared to baseline) after 20 weeks and EOT Extension ▪ maximal postischemic skin blood flow (arbitrary units) during reactive hyperaemia after 5 min of forearm ischemia at 20 weeks and EOT Extension using LDF ▪ change of postischemic skin blood flow (compared to baseline) using LDF ▪ Pulse wave velocity at 20 weeks compared to baseline ▪ laboratory parameter (see above) at 20 weeks and EOT Extension **Additional secondary variable for extension period:** ▪ change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml) at EOT after 52 weeks (EOT Extension)

Original wording Synopsis Statistical methods and 3.5:

Statistical methods	**Efficacy:** ~~The statistical analysis will be done in the intention to treat and per protocol set. The primary parameter will be the maximum FBF at EOT (assessed with venous occlusion plethysmography after forearm ischemia) using an analysis of covariance (ANCOVA) controlling for baseline FBF. Independent t-test will be used to test the parameters between the groups at the time point baseline and EOT as well as the change between baseline and EOT.~~ ~~**Safety:**~~ ~~Analysis of bleeding events and safety parameters is required.~~
Statistical methods	~~**Sample Size Estimation:**~~ ~~The primary variable is change of forearm blood blow with venous occlusion plethysmography (ΔFBF) after forearm ischemia after 20 weeks treatment.~~ ~~The sample size calculation is based on the following assumptions:~~ ~~H0: ΔFBFRiva ≤ ΔFBFASS~~ ~~H1: ΔFBFRiva > ΔFBFASS~~ ~~• Type I error: α = 0.05, one-tailed t-test for independent samples~~ ~~• Power: 1-ß = 0.90~~ ~~• Estimated dropout rate : 25 %~~ ~~• Minimum of expected clinical relevant difference between the groups in changes of maximal forearm blood flow (ΔFBF) = 1.2 ml/100ml with an estimated standard deviation (SD) of σ = 2.4 ml/100ml [Pistrosch, F. et al. Diabetes Care 27: 484-490, 2004]~~ ~~Sample size should be N = 188 Patients (N1/2 = 94 patients per arm) for a valid number of 141 patients for per protocol analysis. This sample size may also provide enough power for further analyses.~~

Revised wording Synopsis Statistical methods and 3.5:

Statistical methods	**Efficacy:** The statistical analysis will be done in the intention to treat and per protocol set. The primary parameter will be the maximum FBF at 20 weeks (assessed with venous occlusion plethysmography after forearm ischemia) controlling for baseline FBF and the Pulse Wave Velocity (PWV) at EOT (extended treatment period after 52 weeks) assessed with a sphygmograph (Mobilograph®, IEM) using an analysis of covariance (ANCOVA). Independent t-test will be used to test the parameters between the groups at the time point as well as the change between baseline and 20 weeks of treatment. Additionally, measurements will be also compared to an extended treatment up to 52 weeks (EOT Extension). **Safety:** ~~Analysis of bleeding events and safety parameters is required.~~
Statistical methods	**Sample Size Estimation:** [...] Additionally, the second primary variable is the difference of PWV between treatment groups at EOT Extension (after 52 week of treatment). The sample size calculation is based on the following assumptions: H0: $PWV_{Riva}=PWV_{ASS}$ H1: $PWV_{Riva}\neq PWV_{ASS}$ ▪ Type I error: α = 0.05, t-test for independent samples ▪ Power: 1-ß = 0.80 ▪ Estimated dropout rate : 20 % ▪ Minimum of expected clinical relevant difference between the groups in PWV = 0.7 m/s with an estimated standard deviation (SD) of σ = 1.0 m/s Sample size should be N=80 patients (40 patients per arm) for a valid number of 66 patients for per protocol analysis. In summary the necessary sample size would be N=188 patients for the study up to week 20 including 80 patients for the extension up to week 52.

Additional wording Introduction (section 1):

[…]

Previous studies demonstrated a fast response of forearm blood flow to interventions (10) however; forearm blood flow is marker of endothelial (dys)function and did not measure structural changes of large conductive arteries or the microvascular bed. In contrast to forearm blood flow changes which occur within a few weeks after an intervention, these structural adaptation of the vascular wall usually require a longer time span.

There are few investigational studies of microvascular skin blood flow in patients with type 2 diabetes which described significant changes during treatment with glucose lowering drugs after 36 weeks (11). However; an extrapolation from the capillary bed to structural changes of large arteries should be difficult due to the different anatomy of the vascular wall. Pulse wave velocity (PWV) as marker of arterial stiffness is an independent predictor of cardiovascular events and mortality (12, 13).

Changes of PWV during medical intervention usually required a longer time span. This had been demonstrated in studies with antihypertensive agents (14) as well as in studies with lipid lowering medication (15) which required treatment periods of at least 12 months to demonstrate an improvement of PWV. We believe that a structural remodeling of the vascular wall in the present investigation also need that period of time.

Changed wording of organizational and administrative aspects (section 3.2):

Coordinating Principal Investigator

PD Dr. Frank Pistrosch

GWT, Study centre, Blasewitzer Str. 43, 01307 Dresden

Tel.: +49 351 4400580

Fax No: +49 351 4400581

Deletion of Substitute Coordination investigator.

Original wording Treatment groups (section 4.2.1):

~~**Arm A: treatment group Rivaroxaban**~~	~~Patients will receive Rivaroxaban 5 mg b.i.d. for the duration of 20 weeks.~~
~~**Arm B: control group aspirin**~~	~~Patients will receive treatment with aspirin 100 mg q.d. for the duration of 20 weeks.~~

~~7 study visits will be performed during the study. Subjects are obliged to come to the study center for 5 visits. Visits will take place at week –2 (screening – V1), day 0 (randomization – V1), at week~~

~~2 (V3), 4 (V4), 8 (V5), 12 (safety/compliance – V6) and week 20 (end of treatment – V7). Visit 4 and Visit 6 will be conducted as a telephone visit.~~

~~Measurements of FBF, LDF and pletysmography at baseline-visit and EOT-visit can be done up to 3 days after the visits in the corresponding study location that provides these measurements. Patients will be informed of the procedure by the physician.~~

Revised wording Treatment groups (section 4.2.1):

Arm A:treatment group **Rivaroxaban**	Patients will receive Rivaroxaban 5 mg b.i.d. for the duration of 20 weeks. Additionally, 80 patients of the study population receive the Rivaroxaban 5 mg b.i.d. for a duration of 52 weeks (extension treatment).
Arm B: control group **Aspirin**	Patients will receive treatment with Aspirin 100 mg q.d. for the duration of 20 weeks. Additionally, 80 patients of the study population receive the Aspirin 100 mg q.d. for a duration of 52 weeks (extension treatment).

7 study visits will be performed during the study. Subjects are obliged to come to the study center for 5 visits. Visits will take place at week –2 (screening – V0), day 0 (randomization/baseline – V1), at week 2 (V2), 4 (V3), 8 (V4), 12 (safety/compliance – V5) and week 20 (end of treatment for the first study period with vascular function test – V6).). Visit 3 and Visit 5 will be conducted as a telephone visit.

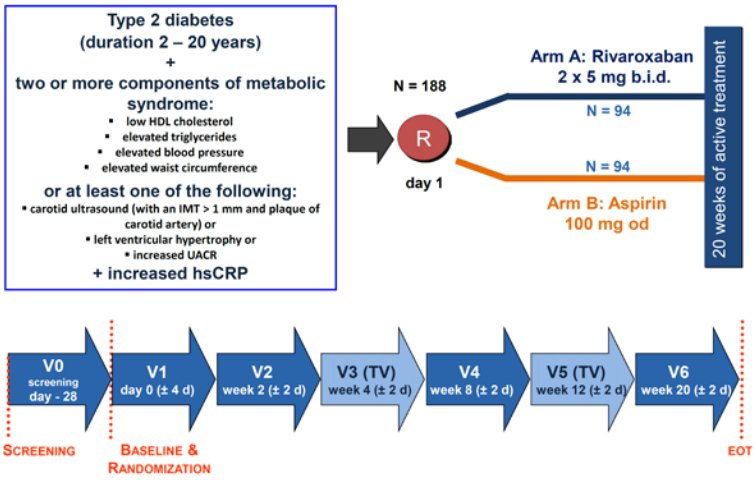
Additionally, 80 patients of the study population will perform 7 additional visits during the extension period. These visits will start after week 20. Patients attending the extension period will perform at all 14 study visits for 8 of these visits they will come to the study center whereas at all 6 visits are performed as telephone visits. The additional visits take place at week 24 (V7), week 28 (V8), week 32 (V9), week 36 (V10), week 40 (V11), week 44 (V12) and week 52 (end of treatment extension - V13). Visit 7, 9, 11 and 12 will be conducted as a telephone visit.

Measurements of FBF, LDF and pletysmography at baseline-visit, visit week 20 (V6) and EOT-visit (V13) can be done up to 3 days after the visits in the corresponding study location that provides these measurements. Patients will be informed of the procedure by the physician.

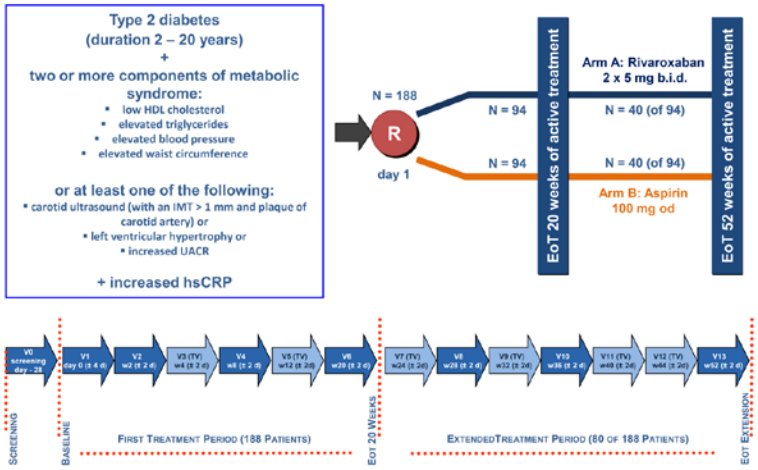
Additional wording Visit schedule (section 4.2.2):

Visit specification	V7 telephone	V8	V9 telephone	V10	V11 telephone	V12 telephone	V13 EOT
week	24	28	32	36	40	44	52
timeframe	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d

Original Flowchart (section 4.2.2):



Changed Flowchart (section 4.2.2):



Additional Visit description (section 4.12.3):

VISIT	V7 (TV)	V8	V9 (TV)	V10	V11 (TV)	V12 (TV)	V13
WEEK	24 (+/- 2 d)	28 (+/- 2 d)	32 (+/- 2 d)	36 (+/- 2 d)	40 (+/- 2 d)	44 (+/- 2 d)	52 (+/- 2 d)
	TREAT	TREAT	TREAT	TREAT	TREAT	TREAT	EOT EXTENSION
STUDY INFORMED CONSENT FOR EXTENSION PERIOD	✓						
VITAL SIGNS (RADIAL PULSE, BLOOD PRESSURE)		✓		✓			✓
BODY HEIGHT							✓
WAIST/HIP CIRCUMFERENCE BODY WEIGHT							✓
CONCOMITANT MEDICATION/ ACUTE DISEASES	✓	✓	✓	✓	✓	✓	✓
ARTERIAL STIFFNESS							✓
FOREARM BLOOD FLOW							✓
INFLAMMATION LABORATORY(1)							✓
SAFETY LABORATORY(3)		✓		✓			✓
EFFICACY LABORATORY(2)							✓
METABOLIC MARKER(4)							✓
LDF INVESTIGATIONS							✓
ADVERSE EVENT REPORTING	✓	✓	✓	✓	✓	✓	✓
DISPENSING/RETURN OF MEDICATION/ DRUG ACCOUNTABILITY		✓		✓			✓

Additional wording of visit description (section 4.14):

Visit 7, Visit 9, Visit 11 and Visit 12 – Extended treatment phase (telephone visits)

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication

Visit 8 and Visit 10 – Extended treatment phase on site visit

The following actions/measures will be performed for patients of Arm A and Arm B:

- assessment of adverse events
- questioning for concomitant medication
- clinical examination for potential bleeding sides
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- return of study medication and drug accountability
- dispense of new study medication
- safety laboratory parameter

Visit EoT of extended treatment period (end of study visit)

The following actions/measures will be performed for patients of Arm A and Arm B:

- questioning for adverse events and concomitant medication
- measurement of blood pressure and heart rate (after resting for at least 3 min in supine position)
- measurement of forearm blood flow
- laserdopplerfluxometry (LDF)
- measurement of arterial stiffness
- efficacy laboratory parameter for endothelial function and coagulation:
- efficacy laboratory for composite of biomarkers of inflammation
- safety laboratory parameter
- assessment of metabolic marker
- return of study drug / drug accountability
- advice patient for further treatment after end of study

Original wording Dispensing of IMP (section 5.7):

~~**Visit**~~ ~~Week~~	~~**V0**~~ ~~**day -28**~~	~~**V1**~~ ~~**day 0** ±4d~~	~~**V2**~~ ~~**2** ±2d~~	~~**V3** (TV)~~ ~~**4** ±2d~~	~~**V4**~~ ~~**8** ±2d~~	~~**V5** (TV)~~ ~~**12** ±2d~~	~~**V6**~~ ~~**20** ±2d~~	~~**Dispensed medication**~~
~~**Rivaroxaban**~~	-	~~90~~ ~~(3 Packs)~~	~~210~~ ~~(7 Packs)~~	-	~~330~~ ~~(11 Packs)~~	-	-	~~630~~
~~**aspirin**~~	-	~~50~~ ~~(1 Pack)~~	~~50~~ ~~(1 Pack)~~	-	~~50~~ ~~(1 Pack)~~	-	-	~~150~~

Revised wording Dispensing of IMP (section 5.7):

Visit Week	**V0** **day -28**	**V1** **day 0** ±4d	**V2** **2** ±2d	**V3(TV)** **4** ±2d	**V4** **8** ±2d	**V5(TV)** **12** ±2d	**V6** **20** ±2d	**Dispensed medication**
Rivaroxaban	-	90 Tabl. (3 Packs)	210 Tabl. (7 Packs)	-	330 Tabl. (11 Packs)	-	*270 Tabl. (9 Packs)*	630 *(+270)* Tabl. = 21 *(+9)* Packs
Aspirin	-	50 Tabl. (1 Pack)	50 Tabl. (1 Pack)	-	50 Tabl. (1 Pack)	-	*100 Tabl. (2 Packs)*	150 *(+100)* Tabl. = 3 *(+2)* Packs

TABLE 12: DRUG DISPENSE FOR FIRST TREATMENT PERIOD (1 PACK RIVAROXABAN CONTAINING 30 TABLETS; 1 PACK ASPIRIN CONTAINING 50 TABLETS);
OPTIONAL: DISPENSE OF IMP AT V6 FOR PATIENTS PARTICIPATIONS TO EXTENDED TREATMENT PERIOD

Visit Week	**V7 (TV)** **24** ±2d	**V8** **28** ±2d	**V9 (TV)** **32** ±2d	**V10** **36** ±2d	**V11 (TV)** **40** ±2d	**V12 (TV)** **44** ±2d	**V13** **52** ±2d	**Dispensed medication**
Rivaroxaban	-	210 Tabl. (7 Packs)	-	510 Tabl. (17 Packs)	-	-	-	720 Tabl. = 24 Packs
Aspirin	-	50 Tabl. (1 Pack)	-	150 Tabl. (3 Packs)	-	-	-	200 Tabl. = 4 Packs

TABLE 13: DRUG DISPENSE FOR EXTENDED TREATMENT PERIOD (80 OF 188 PATIENTS) (1 PACK RIVAROXABAN CONTAINING 30 TABLETS; 1 PACK ASPIRIN CONTAINING 50 TABLETS)

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