Microvascular and anti-inflammatory effects of Rivaroxaban compared to low dose aspirin in type 2 diabetic patients with very high cardiovascular risk and subclinical inflammation (MicroVasc-DIVA)

Statistical Analysis Plan (SAP)

Primary trial objective:	Evaluation of efficacy defined as the 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.		
Trial design:	Multicenter, prospective, active controlled, randomized, 2 parallel arms, open interventional clinical trial		
Investigational medicinal product:	Rivaroxaban	**Comparator:**	Aspirin
Clinical study phase:	Phase IIIb	**Date:**	19.09.2018
EudraCT No.:	2014-001305-41	**Version:**	1.0
Principal Coordinating Investigator:	PD Dr. Frank Pistrosch	**Sponsor**:	GWT-TUD GmbH Dresden - Germany
Statistician:	Dr. Dorothea Schipp		

This SAP is produced on a word-processing system and bears no signatures.

The approval of the SAP is documented in a separate Signature Document.

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Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
b.i.d.	(Bis in Die) twice a day
BMI	Body Mass Index
CI	Confidence Interval
CRNM	Clinical Relevant Non-Major
CSV	Clinically significant value
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronical Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
FBF	Forearm Blood Flow
GmbH	Gesellschaft mit beschränkter Haftung
ICH	International Council for Harmonization
LDF	Laser Doppler Fluxometry
LLOQ	Lower Limit of Quantification
Max	Maximum
Min	Minimum
OR	Odds Ratio
PCSV	Potentially clinically significant value
PPS	Per Protocol Set
PT	Preferred Term
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
q.d.	(quaque die) daily
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SOC	System Organ Class
SOP	Standard Operating Procedure
STD	Standard Deviation
vs.	versus

1 Rational of the statistical analysis plan

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for the MicroVasc-DIVA study.
This plan may be revised during the study to accommodate protocol amendments and to adapt to unexpected issues in study execution or data that affect planned analyses. These revisions will be based on blinded review of the study and data.

2 Investigational Plan

2.1 Study design

This will be a multicenter, 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:

Arm A: treatment group: Rivaroxaban (5 mg b.i.d for the duration of 20 weeks, 52 weeks duration for patients participating in the extension)

Arm B: control group: Aspirin (100 mg q.d. for the duration of 20 weeks, 52 weeks duration for patients participating in the extension)

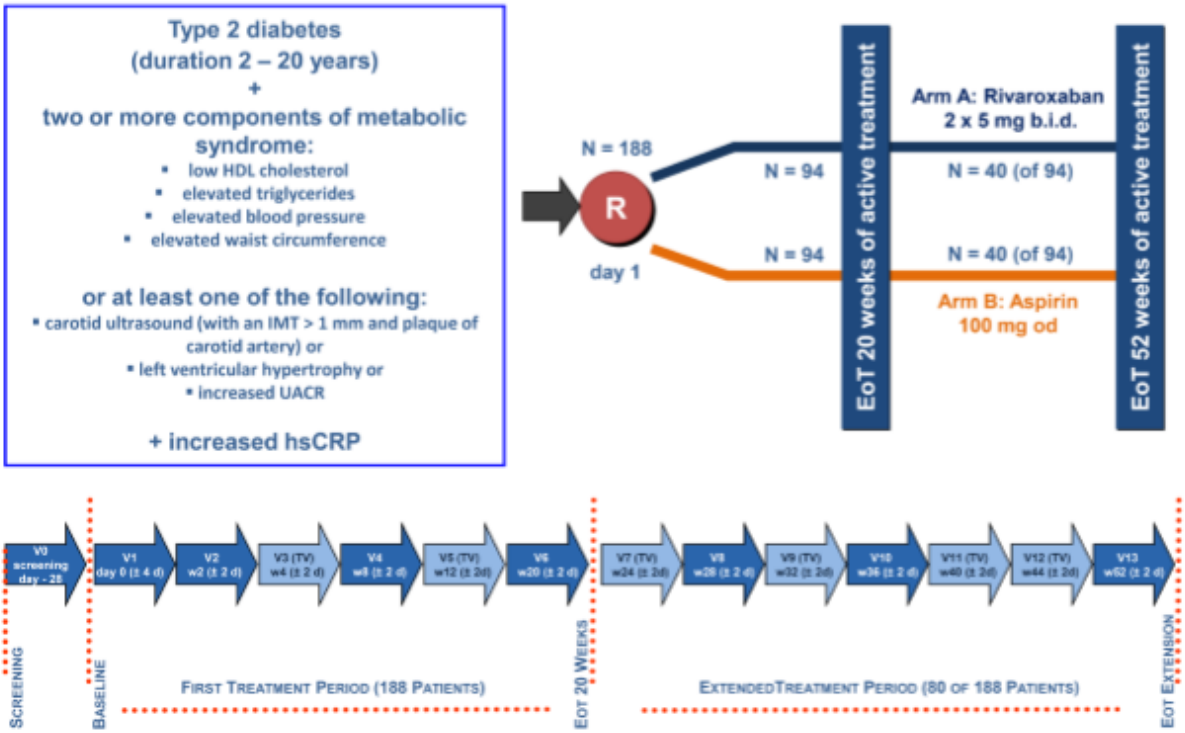

Figure 1: Trial overview

2.2 Visit schedule

7 visits will be performed during the study. 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).

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 performed a total of 14 study 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	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 1: Study visits and parameters

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 2: Study visits and parameters of extended treatment period

2.3 Study objectives

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.

2.3.1 Primary objectives

Primary objective is the 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.

2.3.2 Secondary objectives

- Change of peripheral skin microcirculatory function (measured by Laser Doppler fluxometry; 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-Tnl, 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.

2.3.3 Explorative study objective(s)

Assessment of platelet activation, measurement of mitogenic potential and risk benefit assessment.

2.4 Sample size calculation

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

- Hypotheses: H0: $\mu_{\Delta FBF, Riva} \leq \mu_{\Delta FBF, ASS}$
  H1: $\mu_{\Delta FBF, Riva} > \mu_{\Delta FBF, ASS}$
- Application of t-test for independent samples
- Type I error: $\alpha = 0.05$
- 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 (STD) $\sigma = 2.4$ ml/100ml

Sample size should be at least N = 188 Patients (i.e. N/2 = 94 patients per arm) in order to achieve a valid number of 141 patients (per protocol analysis).

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: $\mu_{PWV, Riva} = \mu_{PWV, ASS}$

- H1: $\mu_{PWV, Riva} \neq \mu_{PWV, ASS}$
- 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 (STD) of $\sigma = 1.0$ m/s

Sample size should be N=80 patients (40 patients per arm) to achieve 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.

3 Analysis Sets

For the analysis, patients not fulfilling the selection criteria of the trial ("all randomized") will be excluded from the statistical analysis. Only casuistic reports will be provided for this group.

3.1 Full Analysis Set (FAS)

For the analysis, patients not fulfilling the selection criteria of the trial ("all randomized") 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, FAS).

3.2 Safety Analysis Set (SAF)

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.

3.3 Per-Protocol Set (PPS)

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 provided complete data of the target variable of interest at the first (V1) and last visit (V6/V13) and who have no major protocol deviations thought to impact the efficacy conclusions of the trial. The classification of protocol violation as major and minor will be done in a data review meeting that will take place after the database is clean.

4 Analysis Variables

4.1 Demographics

The following demographic characteristics will be summarized at baseline day 0:
age (year), gender, race.

4.2 Medical history

Information on following diagnostics will be recorded at baseline day 0:
Pregnancy Test (done yes/no), result of pregnancy test (pregnant yes/no),
ECG (yes/no), if “yes”, ECG result (“normal”, “minor findings”, “major findings”)
Duration of diabetes
In- and exclusion criteria

4.3 Concomitant medication and acute diseases

Medications taken will be recorded from the day of informed consent until the EOT visit (day 0-week 52). Patients who received a concomitant medication at any point of time will be counted in the category “yes”. All patients who did not receive any concomitant medication in the course of the study will be counted in the category “no”.

4.4 Drug administration

The drug amount dispensed and returned will be recorded. Compliance (proportion of drug taken compared to drug dispensed) will be monitored.

4.5 Efficacy Variables

Efficacy variables will be measured at day 0, weeks 20 and week 52:

Forearm blood flow (FBF) (mL/100mL): IR baseline, IR post-ischemic, IR post-ischemic (AUC)

Extension:
Arterial stiffness measured by pulse wave analysis: Pulse wave velocity (m/s), index of augmentation (%), peripheric and central blood pressure systolic/diastolic (mmHg)

Skin blood flow (measured by Laser Doppler):
Depth pre-ischemic blood flow (U), depth post-ischemic blood flow (U), shallow pre-ischemic blood flow (U) and shallow post-ischemic blood flow (U)

4.6 Laboratory Variables

Several categories of laboratory variables are assessed:

- screening laboratory (day -28):
  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

- inflammation laboratory (day 0, weeks 20, 52):
  hsCRP, PAI-1, MCP-1, MPO, IL-6, IL-8, MMP-9, fibrinogen

- efficacy laboratory for endothelial function and coagulation (day 0, weeks 20, 52):
  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 markers (day 0 (if not available, using of values at screening visit), weeks 20, 52):
  HbA_{1c}, triglycerides, LDL-C, HDL-C, total cholesterine

- cardiovascular markers: NT-proBNP, hs-TnI, GDF-15, MR-ANP
- bioassay data (subpopulation at day 0 and week 20): Thrombocytic micro-particles, vasodilator-stimulated phoshoprotein (VASP), serine-positive thrombocytes und thrombocyte proliferation rate.

4.7 Safety Variables

4.7.1 Vital Signs

Vital Signs will be collected in terms of:

Height (cm)	(day 0, week 52)
Weight (kg), BMI (kg/m2), Waist and Hip circumference (cm)	(day 0, weeks 2, 8, 20, 28, 36, 52)
Radial pulse (bpm), systolic/diastolic blood pressure (mmHg)	(day 0, weeks 2, 8, 20, 28, 36, 52)

4.7.2 Safety laboratory

Safety laboratory variables will be monitored (day 0, weeks 2, 8, 20, 28, 36, 52):
hemoglobin, hematocrit, ALAT, ASAT, creatinine (PAP method), blood cell count (leucocytes, erythrocytes, platelets), total bilirubin, sodium, potassium, eGFR

4.7.3 Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from first intake of study medication and then at each visit until the end of the study (day 0-week 52).

Bleedings (yes/no). If “yes” bleeding is classified as:

- major bleeding (“major”)
- clinically relevant non-major bleeding (“CRNM”)

Patients with major bleeding at any time in the course of the study will be counted in the category “major”. All patients with CRNM but never “major” at any time will be counted in the category “CRNM”. Only patients with minor bleedings but never CRNM are counted in the category “minor”.

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

- Seriousness (yes/no):
  Patients with SAE at any time in the course of the study will be counted in the category SAE. All patients with AE but not serious at any time will be counted in the category AE.
- Intensity (mild, moderate, severe)
- Causal relationship (yes/no)
- Action taken with study treatment (drug withdrawn, drug interrupted, dose reduced, dose not changed, dose increased, not applicable, unknown)
- Other specific treatments (none, remedial drug therapy, other)
- Outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, life-threatening, fatal, unknown)

4.8 Definition of derived variables

4.8.1 Primary variable

ΔFBF:
ΔFBF (ml/100ml) will be composed of 5 IR baseline measurements and 8 measurements of post-ischemic blood flow. Repeated measurements for IR baseline per visit will be summarized by arithmetic mean.
Changes in FBF (ml/100ml) will be calculated as IR post-ischemic – IR baseline (mean).

4.8.2 Secondary variables

Skin blood flow (LDF):
Δ Depth: post-ischemic blood flow (depth) – pre-ischemic blood flow (depth)
Δ Shallow: post-ischemic blood flow (shallow) – pre-ischemic blood flow (shallow)

5 Efficacy Endpoints

5.1 Primary endpoint

- Comparison of treatment groups for ΔFBF at week 20

Additional primary variable for extension period:

- Comparison of treatment groups for pulse wave velocity at week 52

5.2 Secondary endpoints

- Comparisons of groups and changes from baseline per treatment group for the following variables:
  - PWV at week 52
  - Maximal difference between baseline and post-ischemic skin blood flow FBF
  - Change of area under the FBF curve over 10 cycles of venous congestion (compared to baseline/day 0) at week 20 and EoT extension
  - Index of augmentation at weeks 20 and 52
  - pulse wave velocity at 20 weeks and EoT Extension compared to baseline
  - 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)
  - laboratory parameters (see above) at weeks 20 and 52

6 Statistical Methods

6.1 Data Handling

Concentrations below the lower limit of quantification will be set to zero by laboratory. In case a set of continuous data contains zeros, an analysis in log scale (as described in 6.3) will be omitted.

6.2 Descriptive or summary statistics

All continuous variables will be summarized by treatment group using the following statistics: n (non-missing sample size), number of missing values (Missing), arithmetic mean (Mean), standard deviation, (STD), median (Median), maximum (Max) and minimum (Min).
Tables for original (untransformed) data will be provided as well as tables for differences from baseline by visit. Boxplots will be presented for illustration.
For nominal or categorical data, frequencies and percentages (based on the non-missing sample size) will be tabulated for each category.

6.3 Hypothesis Testing

Unless otherwise specified all hypotheses will be tested at a 5% level of significance against two-sided alternative hypotheses.

C**ontinuous variables** will be analyzed by the following test procedures:

First of all the assumption of normally distributed data will be checked with Shapiro-Wilk test by treatment group. If the hypothesis of normally distributed data cannot be rejected for both treatment groups treatments will be compared by an ANCOVA procedure which includes “treatment” as the main factor and “baseline value” as covariate. T-Tests for independent samples will be used to compare groups at baseline.

In the event that the normality assumption is not warranted, data will be log-transformed and normality assumption of the transformed data will be checked by Shapiro-Wilk test. In case of non-rejection of the hypothesis of normally distributed data for both treatment groups, ANCOVA procedure and t-tests as described above will be performed on the basis of log-transformed data.

Point estimates and 95% CI of the difference in (adjusted) mean change from baseline will be provided if data are evaluated on basis of an ANCOVA procedure.

Otherwise Mann-Whitney´s-U test on the basis of original data will be applied for comparison of groups at baseline. Mann-Whitney´s-U test on the basis of intra-individual differences to baseline will be applied for treatment comparison per visits after baseline. Wilcoxon´s signed rank test will be applied to evaluate changes from baseline per treatment group.

C**ategorical variables** with 2 categories will be analyzed using Fisher´s exact test (with Yates correction) to compare proportions between treatment groups. Variables with more than 2 categories will be compared by Pearson’s Chi-square test. Additionally for each category, the proportions of treatment groups are compared using an (asymptotic) z test. Significant differences in proportions will be flagged, p-values for the z-test will not be shown.

Missing values will not be imputed.

If necessary, modifications of this general procedure will be described in the following sections of chapter 6.

6.4 Subject Disposition

Subject disposition analyses will be based on all enrolled subjects. The following summaries will be provided:

- Subject disposition, as the number of subjects screened, randomized and completed treatment will be summarized.

The following listings will be provided:

- Listing of subjects withdrawn or dropped out: date of baseline visit, date of the last visit, discontinued by reason
- If there are any protocol deviations, including violation of inclusion/exclusion criteria, and post-enrollment deviations which will impact assessment of efficacy and safety endpoints, a listing will be generated.

6.5 Demographics

Demographic characteristics will be summarized in total and by treatment groups (and center) on the basis of FAS, PPS and SAF. Listings of demographic characteristics will be presented.

6.6 Medical History

Medical history will be summarized for FAS, PPS and SAF by each treatment group. Frequency tables will be provided for pregnancy test and ECG results.

6.7 Concomitant medication and Acute Diseases

Medications taken will be recorded from the day of informed consent until the EOT visit (day 0-week 52). Patients who received a concomitant medication at any point of time will be counted in the category “yes”. All patient who did not receive any concomitant medication in the course of the study will be counted in the category “no”. Number and proportion of subjects taking prior/concomitant medication will be summarized.

6.8 Compliance

The overall treatment compliance will be calculated as: [1- (overall amount of drug dispensed – overall amount of drug returned) / (overall amount of drug dispensed)]x 100%.
In addition to the overall compliance, the treatment compliance will be presented by the following specific ranges for each treatment group: <50%, <80%, ≥80%.
Analysis of compliance will be based on FAS.

6.9 Treatment exposure and observation period

The duration of treatment exposure period during the study is calculated as:

(last drug administration date – first drug administration date) + number of days to next visit after last drug administration.

The duration of observation period during the study is calculated as:

last contact date – randomization date +1.

The duration of exposure and the duration of observation period will be summarized for each treatment group (FAS, PPS and SAF).

6.10 Analysis of baseline characteristics

Baseline data including demographics, anamnestic data, vital signs and laboratory values will be summarized by treatment group. Analyses will be repeated in SAF, FAS and PPS.

6.11 Analysis of Efficacy Endpoints

All efficacy endpoints will be assessed for FAS, PPS and SAF.

6.11.1 Analysis of Primary Endpoint

Primary study endpoint:
The hypothesis H0 is tested against the **one-sided** alternative hypothesis H1

$$H0: \mu_{\Delta FBF,Riva,\ week\ 20} \leq \mu_{\Delta FBF,\ ASS,\ week\ 20} \quad \text{vs.} \quad H1: \mu_{\Delta FBF,\ Riva,\ week\ 20} > \mu_{\Delta FBF,\ ASS,\ week\ 20}$$

by test procedures for continuous data. In case of non-rejection of the normality hypothesis an ANCOVA procedure for repeated measurements will be applied. For repeated measurements per subject an AR(1)-covariance-structure will be specified. Otherwise ANCOVA for repeated measurements will be based on (Blom-transformed) rank data.

Primary endpoint for the extension period:

The hypotheses

$$H0: \mu_{PWV,\ Riva,\ week\ 52} = \mu_{PWV,\ ASS,\ week\ 52} \quad \text{vs.} \quad H1: \mu_{PWV,\ Riva,\ week\ 52} \neq \mu_{PWV,\ ASS,\ week\ 52}$$

will be tested by procedure for continuous data.

Age, gender and duration of diabetes might represent confounding factors and could thus be included as covariates in the statistical model. Models incorporating different combinations of covariates are compared with respect to their model fit. The best fitting model according to the QIC (Quasi-Likelihood information) -criterion will be finally chosen for analysis.

Correction procedures for multiple comparisons are not necessary due to the fact that both primary endpoints consist in single comparisons addressing different variables.

6.11.2 Analysis of Secondary Endpoints

All secondary endpoints will be analyzed according to the procedure for continuous variables. Correlations (original data and changes from baseline) might be calculated.

6.12 Analysis of Safety Data

The summary of safety will be performed based on the SAF.

6.12.1 Vital Signs

Summaries of vital sign variables will include original data and change from baseline by visit.

Blood pressure will be analyzed only by PWA because these measurements are regarded as more precise.

6.12.2 Safety Laboratory Measurements

Summaries of safety laboratory variables will include:

- Descriptive statistics of original values and differences from baseline
- The number (n) and percentage (%) of subjects with CSVs during study, depending on data.

6.12.3 Adverse Events

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

Listings of AEs, SAEs, ADRs and SADRs will be generated. The following variables will be included in the listing:

- Patient ID
- Treatment group
- Age/gender/race
- Verbatim Term
- AE start date and end date/ongoing
- AE Duration
- Study day onset
- Intensity
- Relationship of AE to study drug: unrelated or related
- Action taken
- Treatment
- Outcome

Listing of SADRs resulting in death and study discontinuation will also be generated.

6.12.4 Bleedings

The results for major, CRNM, minor and total bleeding will be documented. Total bleeding includes any bleeding event (including CRNM, minor and major bleeding). These analyses will be performed on SAF and PPS.

6.13 Interim analysis

Interim analyses are not planned.

6.14 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 min and max 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 digits.

7 Appendix: Mock-Up tables, figures and listings

7.1 Subjects Disposition

Patients	Frequencies					
	Total		Rivaroxaban		Aspirin	
	N	%	N	%	N	%
Enrolled						
Screening failures						
Randomized						
Study drug never administered						
Treated						
Did not complete study						
Completed study						

Analysis Set	Frequencies					
	Total		Rivaroxaban		Aspirin	
	N	%	N	%	N	%
FAS						
SAF						
PPS						

Exclusions	Frequencies					
	Total		Rivaroxaban		Aspirin	
from	N	%	N	%	N	%
FAS						
SAF						
PPS						

Reasons for Exclusion from FAS (Screening Failures)	Frequencies					
	Total		Rivaroxaban		Aspirin	
	N	%	N	%	N	%
Study drug never administered						
(all screening failures)						
Study drug never administered						
Non-Compliance						
Data not complete						

Reasons for Exclusion from SAF	Frequencies					
	Total		Rivaroxaban		Aspirin	
	N	%	N	%	N	%
Screening Failure						
Study drug never administered						
…. further reasons …..						

Reasons for Exclusion from PPS	Frequencies					
	Total		Rivaroxaban		Aspirin	
	N	%	N	%	N	%
Screening Failure						
Study drug never administered						
Non-Compliance						
Withdrawal of consent						
Study drug never administered						
Data not complete						
…….. further reasons …..						

7.2 Demographics

Demographics		Frequencies						Hypothesis Testing
		Total		Rivaroxaban		Aspirin		Comparison of Proportions
Variable	Category	N	%	N	%	N	%	p-Value
Gender	Female							
	Male							
Race	European							
	Asian							

Demographics		Original Data										
		Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Age	Rivaroxaban											
	Aspirin											
	Total								-	-	-	-

7.3 Medical History

7.3.1 Medical History

Duration of Diabetes	Original Data										
	Descriptive Statistics							Normality	Comparison of Groups		
Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Rivaroxaban											
Aspirin											

7.3.2 Concomitant medication

Concomitant medication	Frequencies						Comparison of Proportions
	Total		Rivaroxaban		Aspirin		
	N	%	N	%	N	%	p-Value
yes							
no							

7.3.3 ECG and Pregnancy Test

Medical History			Frequencies					
			Total		Rivaroxaban		Aspirin	
Variable	Category		N	%	N	%	N	%
ECG	yes	Normal						
		Abnormal, clinically not significant						
		Abnormal, clinically significant						
		total						
	no							
Pregnancy test done	yes							
	no							

7.4 Compliance

Compliance [%]		Original Data										
		Descriptive Statistics							Normality	Comparison of Groups		
Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Week 2	Rivaroxaban											
	Aspirin											
Week 4	Rivaroxaban											
	Aspirin											
Week 8	Rivaroxaban											
	Aspirin											
Week 20	Rivaroxaban											
	Aspirin											
Week 28	Rivaroxaban											
	Aspirin											
Week 36	Rivaroxaban											
	Aspirin											
Week 52	Rivaroxaban											
	Aspirin											
Overall	Rivaroxaban											
	Aspirin											

Total Compliance	Frequencies						Comparison of Proportions
	Total		Rivaroxaban		Aspirin		
	N	%	N	%	N	%	p-Value
< 50%							
≥ 50% and < 80%							
≥ 80%							

7.5 Treatment exposure and observation period

Duration		Original Data										
		Descriptive Statistics							Normality	Comparison of Groups		
	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Treatment exposure	Rivaroxaban											
	Aspirin											
Observation period	Rivaroxaban											
	Aspirin											

7.6 Efficacy Endpoints

7.6.1 Forearm Blood Flow (FBF)

FBF				Original Data										
				Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Value	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Δ FBF	Day 0	Post1-baseline	Rivaroxaban											
			Aspirin											
		Post2-baseline	Rivaroxaban											
			Aspirin											
		Post3-baseline	Rivaroxaban											
			Aspirin											
		Post4-baseline	Rivaroxaban											
			Aspirin											
		Post5-baseline	Rivaroxaban											
			Aspirin											
		Post6-baseline	Rivaroxaban											
			Aspirin											
		Post7-baseline	Rivaroxaban											
			Aspirin											
		Post8-baseline	Rivaroxaban											
			Aspirin											
	Week 20		Rivaroxaban											
			Aspirin											
	Week 52		Rivaroxaban											
			Aspirin											

FBF			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Max. IR post-ischemic	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											

		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
IR post-ischemic (AUC)	Day 0												
	Week 20												
	Week 52												

Δ FBF (Differenzen zu V0)			Changes from Baseline Day 0												
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups		
Visit	Value	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI
Week 20	Post1-baseline	Rivaroxaban													
		Aspirin													
	Post2-baseline	Rivaroxaban													
		Aspirin													
	Post3-baseline	Rivaroxaban													
		Aspirin													
	Post4-baseline	Rivaroxaban													
		Aspirin													
	Post5-baseline	Rivaroxaban													
		Aspirin													
	Post6-baseline	Rivaroxaban													
		Aspirin													
	Post7-baseline	Rivaroxaban													
		Aspirin													
	Post8-baseline	Rivaroxaban													
		Aspirin													

FBF			Changes from Baseline Day 0													
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups			
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI	
Max. IR post-ischemic	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
IR post-ischemic (AUC)	Week 20															
	Week 52															

7.6.2 Pulse Wave Analysis

PWA			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Pulse Wave Velocity (m/s)	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Index of Augmentation	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
	Day 0	Rivaroxaban											

Peripheral Systolic Blood Pressure		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Peripheral Diastolic Blood Pressure	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Central Systolic Blood Pressure	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Central Diastolic Blood Pressure	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											

PWA			Changes from Baseline Day 0													
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups			
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI	
Pulse Wave Velocity (m/s)	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
Index of Augmenta-tion	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
Peripheral Systolic Blood Pressure	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
Peripheral Diastolic Blood Pressure	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
Central Systolic Blood Pressure	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														
Central Diastolic Blood Pressure	Week 20	Rivaroxaban														
		Aspirin														
	Week 52	Rivaroxaban														
		Aspirin														

7.6.3 Laser Doppler fluxometry (LDF)

LDF			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Δ Depth	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Δ Shallow	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											

LDF			Changes from Baseline Day 0												
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI
Δ Depth	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
Δ Shallow	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													

7.7 Efficacy Laboratory

7.7.1 Inflammation Laboratory

Inflammation Laboratory			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
hsCRP	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban									-	-	-
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
PAI-1	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban									-	-	-
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
……. further variables…..													

Inflammation Laboratory			Changes from Baseline Day 0												
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups		
Variable	Changes	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI
hsCRP	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
PAI-1	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													

……. further variables…..

7.7.2 Laboratory for Endothelian Function and Coagulation

Efficacy Laboratory for Endothelial Function and Coagulation			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
VCAM-1	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban									-	-	-
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
ICAM-1	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban									-	-	-
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
……. further variables…..													

Efficacy Laboratory for Endothelial Function and Coagulation			Changes from Baseline Day 0												
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups		
Variable	Changes	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI
VCAM-1	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
ICAM-1	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
……. further variables…..															

….. similar table for Metabolic Markers and bioassay data ……

7.8 Safety Variables

7.8.1 Vital Signs

Vital Signs			Original Data										
			Descriptive Statistics							Normality	Comparison of Groups at Baseline		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	p-Value	Effect	p-Value	95% CI
Height	Day 0	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban									-	-	-
		Aspirin											
Weight	Day 0	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban									-	-	-
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
Radial Pulse	Day 0	Rivaroxaban											
		Aspirin											
	Week 2	Rivaroxaban									-	-	-
		Aspirin											
	Week 8	Rivaroxaban											
		Aspirin											
	Week 20	Rivaroxaban											
		Aspirin											
	Week 28	Rivaroxaban											
		Aspirin											
	Week 36	Rivaroxaban											
		Aspirin											
	Week 52	Rivaroxaban											
		Aspirin											
…… further variables……													

Vital Signs			Changes from Baseline V1												
			Descriptive Statistics							Comparison to Baseline			Comparison of Groups		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-Value	95% CI	Effect	p-Value	95% CI
Weight	Week 20	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
Radial Pulse	Week 2	Rivaroxaban													
		Aspirin													
	Week 8	Rivaroxaban													
		Aspirin													
	Week 20	Rivaroxaban													
		Aspirin													
	Week 28	Rivaroxaban													
		Aspirin													
	Week 36	Rivaroxaban													
		Aspirin													
	Week 52	Rivaroxaban													
		Aspirin													
…. further variables ……															

7.8.2 Safety Laboratory

Safety Laboratory			Original Data									
			Descriptive Statistics							Comparison of Groups		
Variable	Visit	Treatment	N	Missing	Mean	Median	STD	Min	Max	Effect	p-value	95% CI
Hemoglobin	Day 0	Rivaroxaban										
		Aspirin										
	Week 2	Rivaroxaban										
		Aspirin										
	Week 8	Rivaroxaban										
		Aspirin										
	Week 20	Rivaroxaban										
		Aspirin										
	Week 28	Rivaroxaban										
		Aspirin										
	Week 36	Rivaroxaban										
		Aspirin										
	Week 52	Rivaroxaban										
		Aspirin										

Safety Laboratory CSV's		Frequencies						Comparison of Proportions*
		Total		Rivaroxaban		Aspirin		
		N	%	N	%	N	%	p-Value
Total	Number of Patients							
	Number of Events							
Hemoglobin	Number of Patients							
	Number of Events							
……. further variables…..								

*can only be calculated for number of patients

7.8.3 Adverse Events

Adverse Events		Frequencies						Comparison of Proportions
		Total		Rivaroxaban		Aspirin		
		N	%	N	%	N	%	p-Value
Number of Patients	AE							
	SAE							
	ADR							
	SADR							
Number of Events	AE							-
	SAE							
	ADR							
	SADR							

7.8.4 Bleedings

Bleedings		Frequencies						Comparison of Proportions
		Total		Rivaroxaban		Aspirin		
		N	%	N	%	N	%	p-Value
Number of Patients	Major							
	CRNM							
	Minor							
	Total Bleeding							
Number of Events	Major							-
	CRNM							
	Minor							
	Total Bleeding							-