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Integrated Statistical Analysis Plan

A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (COMPASS - Cardiovascular OutcoMes for People using Anticoagulation StrategieS)

Rivaroxaban for the prevention of major cardiovascular events in CAD or PAD (COMPASS)

Bayer study drug	BAY 59-7939 / Rivaroxaban / Xarelto®		
Study purpose:	Comparative combination drug study for new indication		
Clinical study phase:	III	**Date:**	31 March 2017
Study No.:	BAY 59-7939/15786	**Version:**	4.1

Author:

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PPD (Version 1.0, 2.0, 3.0, 4.1)
PPD (Version 4.1)

This Integrated Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Integrated Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse event
ARB	Angiotensin receptor blockers
bid	Twice daily
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CRF	Case report form (either paper or electronic)
CSR	Clinical study report
CT	Computed tomography
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DSS	Digit Symbol Substitution
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
ESI	Event of special interest
EuroSCORE	European System for Cardiac Operative Risk Evaluation
Hb	Hemoglobin
ICH	International Conference on Harmonization
IPAQ	International Physical Activity Questionnaire
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MRU	Medical resource utilization
NRC	National Research Council
NSAID	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
od	Once daily
PAD	Peripheral artery disease
PASS	Power Analysis and Sample Size software
PPD	PPD
PPI	Proton pump inhibitor
PT	Preferred term
RRR	Relative risk reduction
SAE	Serious adverse event
SAF	Safety analysis set
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitors
TLF	Tables, listings, figures
US FDA	United States Food and Drug Administration
VAS	Visual Analog Scale
VTE	Venous thromboembolism
Xa	Activated coagulation factor X

1. Introduction

Coronary artery disease (CAD) is the most common cause of cardiovascular disease. One-third to one-half of middle-aged males and females in high income countries are expected to develop manifestations of CAD during their lifetime and the number of patients with chronic CAD is rising globally. Coronary heart disease remains responsible for about one-third of deaths in persons over the age of 35 years (WHO, 2008 & 2013).

Peripheral artery disease (PAD) of the lower extremities, while often undiagnosed, is a powerful risk marker of cardiovascular disease (Hirsch et al, 2001). The global prevalence of PAD is less well studied than that of CAD but screening studies suggest that approximately 20% of adults older than 55 years have objective evidence of PAD (Hankey et al, 2006). The severity of PAD is a major determinant of subsequent risk of cardiovascular events and mortality.

Aspirin, statins, and angiotensin converting enzyme (ACE) inhibitors are effective and widely used for the prevention of cardiovascular events in patients with CAD or PAD but the risk of vascular events remains high despite these treatments. A new, safe, and convenient antithrombotic therapy that further improves efficacy when it is added to or replaces aspirin could have a major impact in reducing the individual, community, and global burden of disability and death due to cardiovascular disease.

Rivaroxaban is an orally active anticoagulant that selectively targets activated coagulation factor X (Xa), thereby inhibiting thrombin generation and thrombus formation. Rivaroxaban has been demonstrated in large phase 3 randomized controlled trials to be a highly effective antithrombotic treatment for the prevention and treatment of venous thromboembolism, the prevention of stroke and systemic embolism in patients with atrial fibrillation, and the prevention of major cardiovascular events in patients with recent acute coronary syndrome. The evidence of efficacy of rivaroxaban for the prevention of atherothrombotic events on a background of dual antiplatelet therapy in patients with recent acute coronary syndrome supports the hypothesis that it may also be effective for prevention of atherothrombotic events in patients with established CAD or PAD, receiving usual care.[1]

The study described in this Statistical Analysis Plan (SAP), Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS), is a randomized double-blind trial utilizing a 3 x 2 partial factorial design that will evaluate the efficacy and safety of:

- rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (od) versus aspirin 100 mg daily and
- rivaroxaban 5 mg bid versus aspirin 100 mg od

for the prevention of myocardial infarction, stroke, and cardiovascular death in patients with established CAD or PAD who are receiving standard prevention therapies. The hypotheses are (a) that the combination of rivaroxaban and aspirin compared with aspirin alone will substantially reduce the risk of myocardial infarction, stroke, or cardiovascular death and that this benefit will readily outweigh any potential[2] increase in bleeding and (b) that rivaroxaban compared with aspirin

[1] Text modified as per integrated CSP, Version 2.0.
[2] Text modified as per integrated CSP, Version 2.0.

will reduce the risk of myocardial infarction, stroke, or cardiovascular death and that this benefit will not be accompanied by a clinically relevant increase in major bleeding.

In the (partial factorial) randomization, patients without a continuous[3] need for a proton pump inhibitor will be randomized to receive pantoprazole 40 mg od or placebo for the prevention of major upper gastrointestinal complications.

An independent Data Safety Monitoring Board (DSMB) will monitor efficacy and safety of the studied medications and give recommendations to the steering committee as to whether to continue, modify or stop the study.

This SAP contains definitions of analysis sets, key derived variables, and statistical methods for analysis of efficacy and safety for the COMPASS study. It provides a technical and detailed elaboration of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables. Amendments and/or appendices to this SAP may be used to provide more details on the coding guidelines, data-handling, and output tables and figures. These SAP-associated documents will be finalized ideally 6 months before the planned study end to take into account emerging data external to the trial becoming available during conduct of the trial that could influence study interpretation. All SAP associated documents will be finalized without knowledge of any emerging results by treatment group from the trial.

An amendment of the integrated SAP, Version 3.0, became advisable based on a recommendation received from the DSMB to the Study Chair and Co-Principal Investigators, dated February 06, 2017. The DSMB recommended that treatment arms rivaroxaban 2.5 mg bid + aspirin 100 mg daily, rivaroxaban 5.0 mg bid, and aspirin 100 mg daily be stopped as soon as an orderly close-out of this portion of the COMPASS study could be carried out. The DSMB made this recommendation because they found upon performing the first interim analysis that one of the rivaroxaban arms reached the critical value for early efficacy, as outlined in the DSMB charter. Therefore, the Steering Committee decided to stop the rivaroxaban/aspirin arms of the study for overwhelming efficacy.

The SAP Amendment v3.1, integrated in SAP, Version 4.1, was written fully blinded to the treatment allocation with the intent to fully preserve the statistical analyses that have been outlined in the protocol and the previous version of the SAP. It seeks to clarify some aspects pertaining to the interim analysis and to reflect the wording and additional close-out visits prompted by the premature stop of the anti-thrombotic study treatment arms. In addition, it includes a detailed description of the sensitivity analyses planned to explore the potential impact of missing data on the primary analysis.[4]

This integrated statistical analysis plan for the final analysis of the study is based on the integrated clinical study protocols, Version 3.0, and the integrated SAP, Version 3.0, dated 23 January 2017, which includes Amendment v2.0. All changes to the SAP, Versions 1.0, 2.0, and 3.0, are described in Section 8.

Titles, mock-ups and programming instructions for all statistical output (tables, figures, and listings [TLF]) are provided in a separate TLF specifications document.

[3] Text modified as per integrated CSP, Version 2.0.
[4] Text modified as per integrated SAP, Version 4.1.

2. Study Objectives

Primary objective for rivaroxaban randomization

- To determine whether rivaroxaban 2.5 mg bid + aspirin 100 mg od compared with aspirin 100 mg od reduces the risk of a composite of myocardial infarction, stroke, or cardiovascular death in subjects with CAD or PAD
- To determine whether rivaroxaban 5 mg bid compared with aspirin 100 mg od reduces the risk of a composite of myocardial infarction, stroke, or cardiovascular death in subjects with CAD or PAD

Secondary objectives for rivaroxaban randomization

- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of the composite of major thrombotic events: coronary heart disease death, myocardial infarction, ischemic stroke, and acute limb ischemia, compared with aspirin 100 mg od in subjects with CAD or PAD[5]
- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of the composite of major thrombotic events: cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia, compared with aspirin 100 mg od in subjects with CAD or PAD[6]
- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of mortality compared with aspirin 100 mg od in subjects with CAD or PAD

Tertiary objective for rivaroxaban randomization

- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone preserves the ability to perform everyday activities independently in subjects with CAD or PAD
- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the incidence of hospitalization for any cause compared with aspirin 100 mg od in subjects with CAD or PAD
- To collect medical resource utilization data to be incorporated in economic modeling for subjects with CAD or PAD

Objective for pantoprazole randomization

- To determine whether pantoprazole 40 mg od compared with placebo reduces the risk of upper gastrointestinal bleeding, ulceration, or gastrointestinal obstruction or perforation in subjects with CAD or PAD receiving antithrombotic medications

[5] Text modified as per integrated CSP, Version 3.0.
[6] Text modified as per integrated CSP, Version 3.0.

Objectives for (Day 4-7) post-coronary artery bypass graft (CABG) randomization [7]

- To determine whether each of rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of bypass graft failure compared with aspirin 100 mg od
- To determine the association between post CABG graft failure and risk of a composite of myocardial infarction, stroke, or cardiovascular death in subjects with CAD or PAD

Substudy objectives

The COMPASS-MIND substudy will examine the effect of the antithrombotic therapies being tested in COMPASS on covert cerebral ischemia, thereby providing additional information about mechanisms of disease and treatment benefits.[8] COMPASS-MIND will be conducted concurrently with the main study in a subset of subjects at selected centers.

3. Study Design - Amended[9]

This Phase 3, event-driven (according to the CSP: at least 2,200 subjects with unrefuted[10] primary efficacy outcome events), randomized controlled trial will have a 3 x 2 partial factorial design and will randomize at least 27,400[11] subjects who will receive study treatment for an expected average duration of 3 to 4 years.

The study schedule comprises 4 periods:

- screening,
- run-in,
- follow-up, and
- washout.

The trial will require clinic visits at screening (in most cases this visit is expected to coincide with the run-in visit), run-in, randomization, 1 and 6 months after randomization, and at least every 6 months thereafter until the end of the study. Study staff will contact subjects by phone at Month 3, Month 9, and at the End of Washout Telephone Visit (30 days post Final Follow-up Visit). Some centers may also perform pre-screening visits.

An overview of the procedures conducted in each of these periods is provided in Table 3-2.

[7] Text added as per integrated CSP, Version 2.0.
[8] Text modified as per integrated CSP, Version 3.0.
[9] Text modified as per modification 1 in integrated SAP, Version 4.1.
[10] Text added as per modification 1 in integrated SAP, Version 3.0.
[11] Text modified as per integrated CSP, Version 3.0.

Screening

Screening will be performed to determine subject eligibility and will include the review of inclusion and exclusion criteria, the collection of medical history, physical measurements, and laboratory evaluations.

Run-in

The run-in period will occur during the 28[12] days prior to initiation of randomized study treatment, with the exception of subjects who are randomized after CABG surgery, who will not undergo a run-in phase. During run-in, eligible subjects who have signed informed consent and discontinued any antithrombotic[13] therapy will receive rivaroxaban placebo bid and aspirin 100 mg od. Study pantoprazole or pantoprazole placebo will not be administered during the run-in period.

Randomization

Subjects who have successfully completed the run-in period (intention is to ensure at least 80% adherence to treatment with rivaroxaban placebo bid and aspirin 100 mg od except for extenuating circumstances) and[14] who remain committed to the study as well as those who are being randomized after CABG will be randomized and begin study treatments on Day 1, which will also signal the initiation of the follow-up period. Initially, subjects without a continuous[15] need for treatment with a proton pump inhibitor will be randomized 1:1 to

- pantoprazole 40 mg od or
- matching placebo od,

stratified by center.

All subjects (including those subjects who entered the study while already receiving a proton pump inhibitor) will then be randomized 1:1:1 to anticoagulant therapy stratified by center and by proton pump inhibitor use (randomized to pantoprazole, randomized to pantoprazole placebo, and not randomized, because subject is already taking a proton pump inhibitor) as shown below:

Group A: rivaroxaban 2.5 mg bid + aspirin 100 mg od

Group B: rivaroxaban 5.0 mg bid + aspirin placebo od

Group C: rivaroxaban placebo bid + aspirin 100 mg od

This leads to combinations of randomized study treatment, as displayed in Table 3-1.

[12] Text modified as per integrated CSP, Version 2.0.
[13] Text modified as per integrated CSP, Version 2.0.
[14] Text modified as per integrated CSP, Version 2.0.
[15] Text modified as per integrated CSP, Version 2.0.

Table 3-1. Randomized study treatments*

Treatment Group	Study Treatment Assignments	
A	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo od
B	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole 40 mg od	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole placebo od
C	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo od

*Subjects who have a continuous need for use of a proton pump inhibitor at baseline will undergo only a single randomization (to rivaroxaban 2.5 mg bid + aspirin 100 mg od, rivaroxaban 5 mg bid + aspirin placebo or rivaroxaban placebo + aspirin 100 mg od)

All doses will be provided in tablet form for oral administration. Subjects, site personnel, sponsor personnel, PPD staff (with few exceptions, see protocol), persons performing the assessments, and data analysts (other than the DSMB associated statistician) will remain blinded to the identity of the study treatments from the time of randomization until database lock.

Medical history, concomitant medication, adverse events (AEs), as well as study treatment adherence during the run-in phase will be assessed. Validated questionnaires will be administered to collect data on subject health and quality of life (Standard Assessment of Global-Activities in the Elderly [SAGE], Montreal Cognitive Assessment [MoCA], Digital Symbol Substitution [DSS], European Quality of Life-5 Dimensions [EQ-5D], The Interheart Diet Questionnaire, and The International Physical Activity Questionnaire [IPAQ]), if this information was not yet obtained at the Screening / Run-in Visit.

Follow-up

Subjects will be seen in the clinic at 1 month and at 6 months after randomization and at 6 month intervals thereafter in order to collect information on study treatment adherence, study treatment interruption, outcomes, and adverse events (AEs). Data on the questionnaires will be collected at the Month 24 Visit. The SAGE, MoCA, DSS, and EQ-5D will also be administered at the next study clinic visit after each outcome event.[16] All subjects will be followed for the duration of the study, irrespective of whether they are receiving study treatments or whether an event has occurred. Additional follow-up visits will be conducted by telephone at Months 3 and 9.

Final rivaroxaban/aspirin Follow-up Visit[17]

The primary analysis will be based on the events that occur after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (February 06, 2017, the date of the DSMB recommendation to stop the rivaroxaban/aspirin study treatment arms). At the Final rivaroxaban/aspirin Follow-up Visit, subjects will be asked to stop taking all randomized

[16]Text modified as per integrated CSP, Version 3.0.
[17] Text added as per modification 1 in integrated SAP, Version 4.1.

rivaroxaban and aspirin study treatment, while study treatment with randomized pantoprazole/pantoprazole placebo can continue as planned.

Rivaroxaban/aspirin Washout Telephone Visit[18]

A rivaroxaban/aspirin Washout Telephone Visit will be conducted by telephone about 30 days after the Final rivaroxaban/aspirin Follow-up Visit to collect information on outcomes and protocol specific adverse events.

Note: the rivaroxaban/aspirin Washout Telephone Visit is equivalent to the end of study for those subjects who have not been randomized to pantoprazole/placebo.

Final (pantoprazole/placebo) Follow-up Visit and end of study[19]

The analysis, as pertains to the pantoprazole randomization, will be based on the events that occur after the date and time of randomization and up until the Final Follow-up Visit, also referred to as "Final pantoprazole/placebo Follow-up Visit". Subjects ongoing in the pantoprazole arms will remain in follow-up until the end of study, irrespective of whether they are still taking study treatments or whether they have experienced an outcome. At the Final Follow-up Visit the following information will be obtained from the subject: study treatment adherence, study treatment interruption, outcomes and adverse events, physical measurements and concomitant medications, and questionnaires (except for the Interheart Diet Questionnaire and the IPAQ). Subjects will be asked to stop taking randomized pantoprazole/placebo study treatment. The Final Follow-up Visit (close out is expected to occur over a period of about 3 months)[20] and the subsequent 30-day washout period will occur nearly simultaneously (as scheduling permits) for all study subjects.

End of pantoprazole/placebo Washout Telephone Visit[21]

A pantoprazole/placebo Washout Visit (End of Washout Telephone Visit) will be conducted by telephone about 30 days after the Final pantoprazole/placebo Follow-up Visit to collect information on outcomes and protocol specific adverse events. Adverse events will continue to be collected up to 30 days post study drug treatment with pantoprazole/placebo.

An overview describing these visits and the data to be included in different type of analyses is given in Figure 3-1.

[18] Text added as per modification 1 in integrated SAP, Version 4.1.
[19] Text modified as per modification 1 in integrated SAP, Version 4.1.
[20] Text modified as per integrated CSP, Version 3.0.
[21] Text modified as per modification 1 in integrated SAP, Version 4.1.

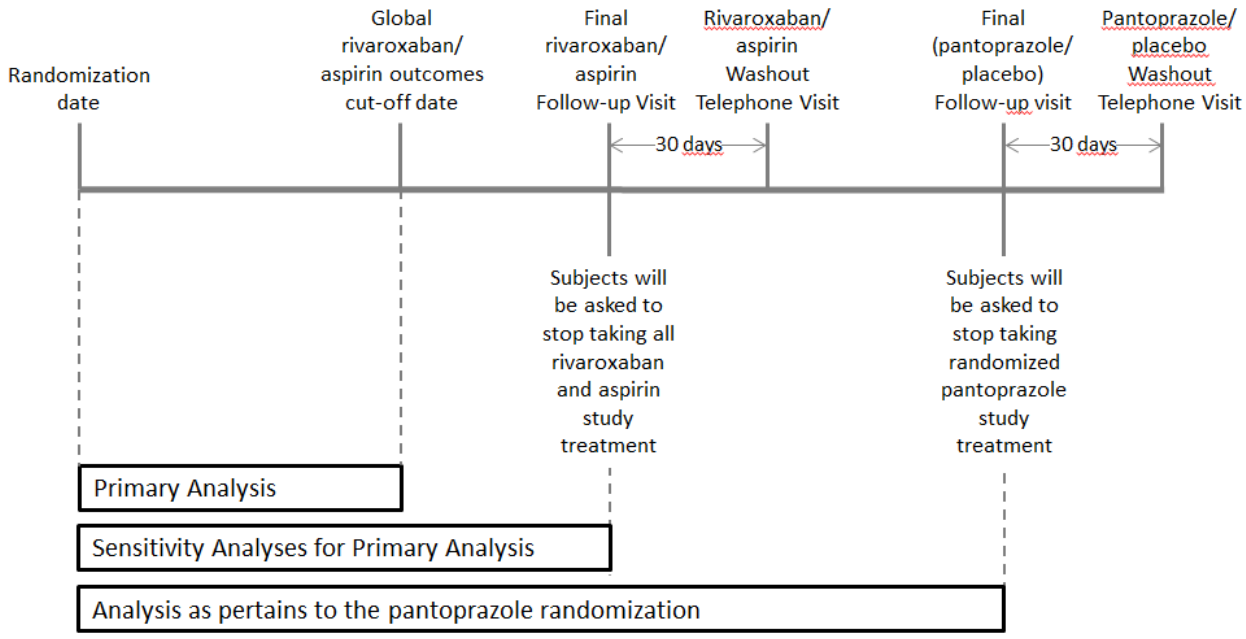

Figure 3-1: **Study visits and analyses**[22]

Premature discontinuation

All subjects will be encouraged to remain on study treatments and under observation for the full duration of the study. If a subject stops taking study treatment early, the reason for this permanent discontinuation will be recorded in the case report form (CRF).

It is important to note that discontinuation of study treatment is not the equivalent to withdrawal of informed consent. Additionally, withdrawal of consent does not withdraw permission to collect vital status. In cases where subjects indicate they do not want to "continue", investigators must determine whether this refers to discontinuation of study treatment (the most common expected scenario), unwillingness to attend follow-up visits, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). *In all cases, including the subjects who have had any of the primary study outcome events, every effort must be made to continue to follow the subject at regular study visits.*[23] *Additionally, survival status and outcome information must be determined for all subjects.*[24]

[22] Figure added as per modification 1 in integrated SAP, Version 4.1.
[23] Text modified as per integrated CSP, Version 3.0.
[24] Text modified as per integrated CSP, Version 2.0.

Table 3-2. Schedule of evaluations[25]

	Pre-Screening[a]	Screening/ Run-in	Randomization[s,26]			Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[n]	Final Rivaroxaban/ aspirin	Rivaroxaban/ aspirin Washout	Final pantoprazole /placebo	Final Pantoprazole/ placebo Washout
Timing		-4w	0	1 m	3m[m]	6m	9m[m]	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		30d post Final Rivaroxaban/ aspirin[m]		1 m post Final pantoprazole /placebo[m]
Windows[q,26]			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w		± 5d	± 4w	± 5d
Informed consent (if required for pre-screening)	X																			
Informed consent		X[r,26]																		
Inclusion/exclusion criteria	X	X	X[26]																	
Demographics		X																		
Medical history			X																	
Physical measurements[b]		X								X							X		X	
Concomitant medications		X	X							X							X		X	
Pregnancy test if pre-menopausal		X																		
Laboratory tests[c]		X[d]	X[e]																	

[25] Table modified as per integrated CSP, Versions 2.0 and 3.0 and modification 1 in SAP, Version 4.0.
[26] Added as per Amendment 6. (See Section 13.1.2)

	Pre-Screening[a]	Screening/ Run-in	Randomization[s,26]			Follow-up													Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[n]	Final Rivaroxaban/ aspirin	Rivaroxaban/ aspirin Washout	Final pantoprazole /placebo	~~Final~~ Pantoprazole/ placebo Washout
Timing		-4w	0	1 m	3m[m]	6m	9m[m]	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		30d post Final Rivaroxaban/ aspirin[m]		1 m post Final pantoprazole /placebo[m]
Windows[q,26]			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w		± 5d	± 4w	± 5d
Blood/DNA collection and storage			X[f]	X[f]																
Diet and activity questionnaires		X[o]	X[o]	X[p,27]						X										
MoCA, DSS, and SAGE [t, 28]		X[o]	X[o]	X[p,27]						X							X		X	
EQ-5D[g]		X[o]	X[o]	X[p,27]						X							X		X	
Health Care Costs			X																	
Driving Status			X																	
EuroSCORE for subjects randomized post CABG surgery			X																	
CT coronary angiography[h]								X[h]									X			
MRI brain[i]			X														X		~~X~~	
Outcomes			X[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X[k]	X[l]			X		X	X	X	X	X	X	X	X	X	X[u]			

[27] Added as per Amendment 6. (See Section 13.1.2)

[28] Footnote added as per Amendment 8 (See Section 13.3.3)

	Pre-Screening[a]	Screening/ Run-in	Randomization[s,26]			Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[n]	Final Rivaroxaban/ aspirin	Rivaroxaban/ aspirin Washout	Final pantoprazole /placebo	~~Final~~ Pantoprazole/ placebo Washout
Timing		-4w	0	1 m	3m[m]	6m	9m[m]	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		30d post Final Rivaroxaban/ aspirin[m]		1 m post Final pantoprazole /placebo[m]
Windows[q,26]			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w		± 5d	± 4w	± 5d
Study drug adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X[u]	
Study drug accountability			X	X		X		X	X	X	X	X	X	X	X	X	X			X[u]	

Abbreviations: w = week; m = month; y = year; d = day; DNA = deoxyribonucleic acid; MoCA = Montreal Cognitive Assessment; DSS = Digit Symbol Substitution test; SAGE = Standard Assessment of Global-Activities in the Elderly; EQ-5D = European Quality of Life-5 Dimensions questionnaire; CT = computed tomography; MRI = magnetic resonance imaging; CABG = coronary artery bypass graft

a. Pre-screening visit is not mandatory and will be conducted only in some centers and for some subjects. Subjects who will be randomized Day 4-7 after CABG surgery do not require pre-screening.
b. Weight, height, waist and hip circumference, heart rate, ankle-brachial blood pressure index
c. Serum creatinine, total cholesterol
d. If not available within 1 year prior.
e. Repeat serum creatinine in patients being enrolled Day 4-7 post CABG surgery. For other, non-CABG subjects, the blood results of creatinine and total cholesterol should be available within 3 months of this visit.
f. Collection of blood & DNA samples for central evaluation in subjects participating in the COMPASS-MIND substudy is optional. If collected, obtain samples at randomization, before starting the study drug, and at 1 month, or as close to one month after randomization as possible. If the first blood sample is not collected before start of study drug, it is not required. Irrespective of whether the first blood sample is obtained, collect the second blood sample at 1 month. If either the DNA sample or second blood sample is missed, it should be collected at the next visit.
g. Using the European Quality of Life-5 Dimensions questionnaire and to be performed at screening/run-in or randomization (see “o”), year 2 and Final Follow-up Visit as well as at the next study clinic visit after each outcome event

h. CT angiography will be performed at 1 year or later in all subjects who are randomized Day 4-7 after CABG to evaluate graft patency (except in subjects those with specific contraindications). In the event the subject undergoes an invasive coronary angiography at 1 year or later post CABG for any reason, a CT angiogram may not be required.
i. MRI of the brain will be performed only in COMPASS-MIND substudy subjects after randomization and near the end of the follow-up
j. Adverse events will be assessed from time of consent to 30 days post last dose of study treatment
k. Stop treatment with non-study aspirin. Dispense run-in medications. CABG surgery patients will be randomized Day 4-7 after CABG surgery and will not be dispensed run-in study drug; however, the Screening/Run-In Visit CRFs are still required to be completed for these subjects.
l. Stop run-in medication and begin randomized treatment assignment
m. Telephone visits
n. Visits will continue every 6 months until the required number of primary efficacy outcomes has been collected
o. It is optional to administer all or some of the questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) at Screening/Run-in instead of at the Randomization Visit, or as soon as possible thereafter (with the exception of patients randomized Day 4-7 post CABG; see “p”).
p. For patients randomized Day 4-7 post CABG, questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) should be performed at the 1 month visit.
q. Clinic visits should be scheduled as close to the specified interval as possible, and preferably within the defined window. If it is not possible for the subject to return within the visit "window," especially due to unforeseen circumstance beyond the control of the subject or the study center, then the visit should be scheduled as close to the interval as is convenient for the subject and study center.
r. CABG subjects can sign the informed consent before or after surgery.
s. CABG subjects should be randomized between Day 4-7 after the surgery. In the event that a subject is unable to be randomized within this time range for medical and logistical reasons, the subject can be randomized, up to Day 14 post-CABG.
t. Also to be administered at the next study clinic visit after each outcome event.
u. Pantoprazole/pantoprazole placebo study treatment only.

4. General Statistical Considerations

4.1 General Principles - Amended

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles (inter quartile range), median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Primary outcome events (myocardial infarction, stroke, CV death), selected secondary and tertiary outcome events (acute limb ischemia, heart failure, venous thromboembolism, cancer), as well as bleeding and GI events will undergo an event adjudication process to evaluate whether events reported by investigators meet the pre-specified trial definitions. A reported and adjudicated event is designated "unrefuted" if it does meet the specified definition or "refuted" if it does not. Primary statistical analyses will be based on unrefuted events. In addition, all reported events will summarized. [29]

4.2 Handling of Non-compliance to Study Treatment or Follow up[30]

A subject who signed an informed consent form, and, for any reason (e.g., failure to satisfy the in- and exclusion criteria) terminates the study without dispensation of run-in study drug and without run-in exemption for peri-operative CABG, is regarded as a "screening failure".

A subject who signed an informed consent form and either received run-in study drug or was scheduled for randomization after peri-operative CABG surgery, and, for any reason (e.g., non-compliance during run-in phase or failure to satisfy the in- and exclusion criteria) terminates the study before randomization, is regarded as a "run-in phase failure".

A randomized subject who permanently stops taking study treatment before their Final rivaroxaban/aspirin Follow-up Visit (for rivaroxaban/aspirin) or their Final pantoprazole/placebo Follow-up Visit (for pantoprazole/placebo) for any reason is defined as having had a premature permanent discontinuation of study treatment (including subjects who were randomized but never started taking any study treatment). The reason for permanent discontinuation of study treatments will be recorded in the CRF. Subjects who continued on rivaroxaban/aspirin study treatment until the global rivaroxaban/aspirin outcomes cut-off date but stopped rivaroxaban/aspirin study treatment before their Final rivaroxaban/aspirin Follow-up Visit will still be considered as study rivaroxaban/aspirin follow-up completers.

However, all subjects will be encouraged to remain on their randomized and pertinent (to the portion of the study) study treatments and under observation until the end of the study. Discontinuation of study treatment is not the equivalent to withdrawal of informed consent. In cases where subjects indicate they do not want to "continue", investigators must determine whether this refers to discontinuation of study treatment, unwillingness to attend follow-up visits, unwillingness to have

[29] Text added as per modification 1 in integrated SAP, Version 3.0.
[30] Text modified as per modification 1 in integrated SAP, Version 4.1.

telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). Every effort will be made to continue to follow the subject. Additionally, survival status and outcome information must be determined for all subjects at the end of the study.[31] The expectation is that only very few subjects will have incomplete follow-up (in any form) within this trial.

A subject will be declared to have incomplete follow-up or to be lost to follow-up (i.e., to be completely non-compliant to follow-up) if, despite of all possible efforts, all investigators, dedicated site staff, the National Leader's Office and/or PPD Project Office (as applicable and as local regulations allow) are not able to contact the subject or to retrieve information about the subject from[32] a third party (e.g., family member, doctor). Every possible effort will be made to contact the subject or a third party and to determine the endpoint and survival status and reason for discontinuation as local law permits. If it is documented in the database that the subject is alive at the global rivaroxaban/aspirin outcomes cut-off date / at the end of the study, the subject will not be classified as lost to follow-up, but as alive.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the CRF including best estimate dates of site investigators (see below) collected in the clinical database.

All efforts will be made to collect complete data for all subjects randomized in this study. Subjects will be followed to the study end and will complete all required data collection, regardless of their compliance with study medications or visits.

Missing or incomplete event dates

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year, or at least the date when the subject was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the subject prior to the event and the date of contact when information about the event was known. This method for date estimation has been used in many studies and is recommended by Dubois and Hebert (2001) (6).

If the site investigator does not provide a best estimate as to when the event occurred, the study team at PPD will follow the above rules to estimate the event date. If the date/time information is not sufficient to determine whether an event occurred prior or after randomization, the event is

[31] Text modified as per integrated CSP, Version 2.0.
[32] Text modified as per SAP amendment 1.0.

considered as an outcome, to be conservative. The event start date will be imputed no earlier than randomization date.

4.4 Interim Analyses and Data Monitoring

Interim assessments and study monitoring for efficacy and safety will be done by an independent DSMB, which will review unblinded event rates. An independent statistician within PPD who is not involved with any study conduct, will perform interim data analyses to support the DSMB. The description below is largely according to the study protocol. Any further details of the interim analyses will be specified in a separate interim statistical analysis plan and/or the DSMB charter.

Two formal interim analyses are planned when 50% (about 1,100) and 75% (about 1,650) of the expected number of accumulated primary efficacy outcome events (2,200 subjects with an unrefuted[33] event) accrue.

If the interim analyses show clear and consistent benefit in both rivaroxaban treatment groups, the DSMB may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of some or all of the study treatment groups: a reduction of 4 standard deviations in the analysis of the primary efficacy outcome at the first interim analysis (one-sided p-value < 0.0001) or 3 standard deviations at the second interim analysis (one-sided p-value < 0.0014). If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be done after at least an additional 3-6 months[34] to confirm the boundary remains crossed and that the trend in treatment effect is not temporary.

For a lack of efficacy, a futility approach will be utilized at the time of planned interim analysis. If the conditional probability of rejecting the null hypothesis for either primary comparisons, given current trends, falls to an unacceptably low level (i.e., <5%), the DSMB may consider recommending early termination of the study.

Given these conservative monitoring boundaries and only 2 interim analyses, the type I error level adjustment for the final analysis will be negligible.

If the results are clear with one intervention, but not for the second intervention, the DSMB may decide to continue evaluation of both or one rivaroxaban treatment arms. If the study is continued with both interventions, then the type I error levels specified in Section 6.2 will be used in the final analysis; if the decision is made to continue with only one intervention, the final comparison will be made as follows:[35]

- If one intervention was stopped early for efficacy, the multiple testing procedure for the final analysis will be performed as described in Section 6.2 with the assumption that the p-value for the primary efficacy outcome of the arm that was stopped early for overwhelming efficacy is smaller than 0.025. For secondary outcomes, the p-values will be obtained from log-rank tests based on all available data for the stopped arm (data from confirmation analysis 6 months after respective interim look) and the complete data from the comparator arm.

[33] Text added as per modification 1 in integrated SAP, Version 3.0.
[34] Text modified as per modification 3 in integrated SAP, Version 3.0.
[35] Text modified as per integrated CSP, Version 3.0.

- If one intervention was stopped early for futility, the final analysis will be performed when at least 1,513* subjects in the two remaining arms have experienced an event.
  The final analysis will be performed according to the multiple testing strategy as described in in Section 6.2. P-values for the primary and secondary hypotheses for the intervention stopped early will be obtained from the log-rank tests based on all available data for the stopped arm and the complete data from the comparator arm. It can be assumed that for the stopped intervention the corresponding p-value of the primary efficacy outcome will be greater than 0.05. Thus, for the intervention stopped early for futility the primary and none of the secondary outcomes can achieve statistical significance at the overall type I error level of 5%.

  *The whole study was planned to be stopped when at least 2,200 subjects had experienced an unrefuted[36] primary outcome event. Under the planning assumptions that both alternative hypotheses are true, observed randomization times and estimated overall incidence rates based on preliminary data, and projected study duration after sample size increase, it is expected that 826 subjects in the control arm and each 687 subjects in the rivaroxaban intervention arms will experience a primary outcome event. Dropping one intervention arm early but still expecting that for the other comparison the alternative hypothesis holds true, the study needs to be continued until at least 826 + 687 = 1,513 subjects in the remaining arms have experienced a primary event.

The steering committee will review overall blinded event rates to ensure that they meet protocol projections. If overall event rates are lower than expected, consideration will be given to increasing the sample size or extending the study duration without knowledge of any treatment effect. The trial will aim to enroll about one-quarter subjects with PAD[37]; this will be monitored during the trial and steps may be taken to adjust the proportion during the trial.

The analyses to be performed for the interim analyses include analyses for the primary and secondary efficacy outcomes, the primary safety outcome and other safety outcome analyses, and adverse events of special interest. In addition, any analyses requested by the DSMB will be performed to assess the efficacy and safety of all study treatments. In addition to these formal interim analyses, the DSMB may regularly review unblinded data as outlined in the DSMB charter.

4.5 Data Rules - Amended[38]

4.5.1 Analysis Dates

A common trial close-out window and a close out (cut-off) date will be chosen by a study committee for the COMPASS trial. All subjects will return to the clinic for a Final Follow-Up Visit within this pre-specified acceptable close-out time-window (about 3 months[39]; period ends with the common trial close-out date, see below).

Based on the DSMB recommendation after the first interim analysis and the early close-out of the rivaroxaban/aspirin study treatment portion of the study, some of the previously defined analysis dates became less important or dispensable for the rivaroxaban/aspirin randomization, while additional dates had to be added.

[36] Text added as per modification 1 in integrated SAP, Version 3.0.
[37] Text modified as per integrated CSP, Version 3.0.
[38] Text modified as per modification 1 in integrated SAP, Version 4.1.
[39] Text modified as per integrated CSP, Version 3.0.

- Rivaroxaban/aspirin arms close-out window:
  The pre-specified target calendar date range within which subjects are to return to the clinic for a Final rivaroxaban/aspirin Follow-up Visit planned to range from end of February 2017 to 15 May 2017.
- Global rivaroxaban/aspirin outcomes cut-off date:
  The global rivaroxaban/aspirin outcomes cut-off date is 06 February 2017, i.e., the date when the DSMB recommended to stop the study treatment arms rivaroxaban 2.5 mg bid + aspirin 100 mg daily, rivaroxaban 5.0 mg bid, and aspirin 100 mg daily as soon as an orderly close-out of this portion of the study could be carried out. Outcome events that occur up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) will be counted in the primary analysis, otherwise the subject will be censored at the global rivaroxaban/aspirin outcomes cut-off date.
- Common trial close-out window:
  The pre-specified acceptable calendar date range within which subjects ongoing in the pantoprazole/placebo portion of the study are to return to the clinic for a Final Follow-Up Visit (e.g. about 3 months).
- Common trial close-out date:
  The common trial close out (cut-off) date is the end date of the common trial close-out window. It is the last calendar date acceptable for counting events, prior to the washout period.
  If a subject who is unable to attend his/her Final Follow-up Visit within the acceptable common trial close-out time-window, has a trial-related contact after the common trial close-out date, the observation period up until the common trial close-out date (inclusive) will be considered in the analysis.

For each subject, the following individual analysis dates will be derived:

- Randomization date:
  The date of randomization to antithrombotic treatment of the subject.
- Date of the Final rivaroxaban/aspirin Follow-up Visit:
  The date of the Final rivaroxaban/aspirin Follow-up Visit for the individual subject.
  If subjects do not have a Final rivaroxaban/aspirin Follow-up Visit, the date will be missing.
- Final (pantoprazole/placebo) Follow-Up Visit date:
  The date of the Final (pantoprazole/placebo) Follow-Up Visit for the individual subject.
  Beginning with the announcement of trial close-out, all subjects ongoing in the pantoprazole/placebo portion of the study are to return to the clinic for their Final Follow-Up Visit within the pre-specified common trial close-out window (see Section 3 for the schedule of evaluations at the Follow-Up Visit). If subjects do not have a Final Follow-Up Visit, the date will be missing.
- Rivaroxaban/aspirin Washout Telephone Visit date:
  The date of the rivaroxaban/aspirin Washout Telephone Visit for the individual subject. To be performed about 30 days after the Final rivaroxaban/aspirin Follow-up Visit.

- End of pantoprazole/placebo Washout (Telephone) Visit date:
  The date of the End of pantoprazole/placebo Washout Visit for the individual subject.
  To be performed about 30 days after the Final pantoprazole/placebo Follow-up Visit.
  If subjects do not have an End of pantoprazole/placebo Washout Visit, the date will be missing.
- Last contact date during rivaroxaban/aspirin portion of the study:
  The date of the last documented contact with the subject or a third party up until the maximum (later) of the subject's {date of the Final rivaroxaban/aspirin Follow-up Visit, end of rivaroxaban/aspirin Washout date}. For subjects who died after randomization but before their scheduled end of rivaroxaban/aspirin Washout date, the date of the last rivaroxaban/aspirin related contact is set to the death date.
- Date of the last follow-up contact:
  The date of the last known documented contact with the subject or a third party (including data on subject survival status)
  - up until the Final Follow-up Visit date (inclusive), if the subject attends his/her Final Follow-up Visit or
  - up until the common trial close-out date, if the subject does not attend his/her Final Follow-up Visit.
  For subjects who die (a) after randomization but before the beginning of the common trial close-out window or (b) during the common trial close-out window but before their Final Follow-up Visit takes place, the date of the last follow-up contact is set to the death date.
  This date is only applicable to analyses for pantoprazole/placebo comparisons at the end of the study.
- Date of the last trial contact:
  The date of the last known documented contact with the subject or a third party (including data on subject survival status).
- Date of last double-blind dose of antithrombotic study treatment:
  The later date of
  - the last dose of rivaroxaban/rivaroxaban placebo study medication and
  - the last dose of aspirin / aspirin placebo study medication.
  For a subject with premature permanent discontinuation of any study medication, the corresponding last dose date(s) will be obtained from the Permanent Discontinuation CRF Report. If study medication was continued until the Final rivaroxaban/aspirin Follow-up Visit, the date of the last dose of the corresponding study treatment will be the date of the Final rivaroxaban/aspirin Follow-up Visit.
  If missing or incomplete, the date of last double-blind dose of antithrombotic study treatment is set to the latest logically possible date of antithrombotic study medication administration on or before the earliest of the subject's following dates, the date of the last contact for the rivaroxaban/aspirin comparison, the date of death, or the end of the rivaroxaban/aspirin arms close-out window, and no earlier than the randomization date.
- Date of last double-blind dose of pantoprazole study treatment:
  The date of the last dose of pantoprazole / pantoprazole placebo study medication of a subject randomized to pantoprazole.

For a subject with premature permanent discontinuation of pantoprazole/pantoprazole placebo study medication, the last dose date will be obtained from the Permanent Discontinuation CRF Report. If pantoprazole/pantoprazole placebo study medication was continued until the Final Follow-up Visit, the date of the last dose of pantoprazole / pantoprazole placebo study medication will be the date of the Final Follow-up Visit.
If missing or incomplete, the date of last double-blind dose of pantoprazole study treatment is set to the latest logically possible date of pantoprazole study medication administration on or before the earliest of the subject's following dates, the date of last follow-up contact, the date of death, or the common trial close-out date, and no earlier than the randomization date.

4.5.2 Data Scopes

The analysis, as pertains to the rivaroxaban/aspirin randomization, will be based on all data collected for a randomized subject until end of the rivaroxaban/aspirin portion of the study, or until the time of loss to follow-up with no indication that the subject returned, or complete refusal to provide additional information.

The analysis, as pertains to the pantoprazole/placebo randomization, will be based on all data collected for a randomized subject until end of study, or until the time of loss to follow-up, or complete refusal to provide additional information.[40]

This section describes the coverage of the event data scopes used for the statistical analyses. Analysis sets are described in Section 5.

Data scope for rivaroxaban/aspirin randomization according to intention-to-treat principle

For the rivaroxaban/aspirin comparisons performed after the DSMB recommendation related to the results of the first interim analysis, analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see Section 5.1.1) and will include all outcome events that occur after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) for each subject. Events occurring after the global rivaroxaban/aspirin outcomes cut-off date will not be counted for primary analysis (see also Section 4.5.1). Subjects will be kept in the study group to which they were randomized. This ITT data scope will be applied to the analysis of the primary efficacy and safety variables, following the intention-to-treat principle. ("ITT" data scope)

Additional data scopes for the rivaroxaban/aspirin randomization

Sensitivity analyses for the primary efficacy outcomes will be based on all outcome events occurring after the date and time of randomization and up until the Final rivaroxaban/aspirin Follow-up Visit (inclusive) for each subject. ("Rivaroxaban/aspirin Follow-up" data scope)

Data scope for the pantoprazole/placebo randomization according to intention-to-treat principle

Analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see Section 5.1.1) and will include all outcome events that occur after the date and time of randomization and up until the Final Follow-up Visit (inclusive) for each subject. For subjects

[40] Text modified as per modification 2 in integrated SAP, Version 3.0.

who are unable to attend the Final Follow-up Visit within the acceptable common close-out time-window (range of dates from announcement of trial close-out up to the common trial close-out date), events occurring after the common trial close-out date will not be counted (see also Section 4.5.1). Subjects will be kept in the study group to which they were randomized and the follow-up period for each subject will be as long and complete as possible.

Additional data scopes for secondary safety analyses for the rivaroxaban/aspirin randomization

Additional secondary analyses of safety outcomes will be based on the safety analysis set (see Section 5.1.2). Subjects will be kept in the study group to which they were randomized. Additional data scopes will be defined to include all outcome events as follows:

- All outcome events for each subject occurring after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) ("ITT" data scope)
- All outcome events occurring after the date and time of randomization and up until 2 days following permanent discontinuation of double-blind antithrombotic study treatment documented in the database ("treatment emergent outcomes" data scope)
- All outcome events occurring after the date and time of randomization and up until 30 days following permanent discontinuation of double-blind antithrombotic study treatment documented in the database ("plus 30 days safety" data scope)
- All outcome events occurring after the date and time of randomization during the entire individual rivaroxaban/aspirin follow-up and wash-out periods documented in the database ("Rivaroxaban/aspirin Follow up + Wash out" data scope)

Data scopes for safety analyses for the pantoprazole/placebo randomization

Analyses of safety outcomes for the pantoprazole randomization will be based on the safety analysis set related to the pantoprazole randomization. Subjects will be kept in the study group to which they were randomized. The outcome events will include:

- All outcome events observed from randomization until 2 days following permanent discontinuation of the pantoprazole study drug ("treatment emergent outcomes" analysis)
- All outcome events observed from randomization during the entire follow-up and wash-out periods up until the end of the trial

Corresponding censoring rules are described in Section 4.5.3.

4.5.3 Censoring Rules for Time-to-Event Variables

For any time-to-event variable in this study, the following censoring rules will be applied:

Censoring rules for analyses related to the rivaroxaban/aspirin randomization according to the intention-to-treat principle

- For analyses according to the intention-to-treat principle which are related to the rivaroxaban/aspirin randomization and performed after the DSMB recommendation, randomized subjects without documentation of an evaluable event will be censored at

- the minimum (earliest) of the global rivaroxaban/aspirin outcomes cut-off date and the subject's last contact date during the rivaroxaban/aspirin portion of the study.

This censoring rule will be applied to all analyses according to the intention-to-treat principle. In the rare event that for a subject only survival status information can be retrieved at the end of the study rivaroxaban/aspirin portion of the trial but no information on other outcomes, the last study rivaroxaban/aspirin follow-up contact where survival status information was obtained will still be used to determine the censoring date for the subject and if there were no known events up to then the subject will be considered as event-free.

Censoring rules for analyses related to the pantoprazole/placebo randomization according to the intention-to-treat principle

- For analyses according to the intention-to-treat principle, randomized subjects without documentation of an outcome[41] event will be censored at
  - the subject's Final Follow-Up Visit if the subject attends the Final Follow-Up Visit before the common trial close-out date.
  - the subject's date of last follow-up contact up to the common trial close-out date (inclusive) if (a) the subject does not attend his/her Final Follow-Up Visit before the common trial close-out date and (b) the subject's date of last trial contact is not after the common trial close-out date.
  - the common trial close-out date if (a) the subject does not attend his/her Final Follow-Up Visit before the common trial close-out date and(b) the subject's date of last trial contact is after the common trial close-out date.

  This censoring rule will be applied to all analyses related to the pantoprazole/placebo randomization performed after common trial close-out according to the intention-to-treat principle. In the rare event that for a subject only survival status information can be retrieved at the end of the study but no information on other outcomes, the last follow-up / trial contact where survival status information was obtained will still be used to determine the censoring date for the subject and if there were no known events up to then the subject will be considered as event-free.

Censoring rules for secondary safety analyses related to the rivaroxaban/aspirin randomization

- For secondary safety analyses based on the safety analysis set and the ITT data scope, all randomized subjects with at least one dose of either randomized study medication and without documentation of an outcome[42] event within the ITT data scope will be censored as stated above for study rivaroxaban/aspirin analyses according to the ITT principle.
- For "treatment-emergent" secondary safety analyses, all randomized subjects with at least one dose of study medication and without documentation of an outcome[43] event within the

[41] Text modified as per modification 1 in integrated SAP, Version 3.0.
[42] Text modified as per modification 1 in integrated SAP, Version 3.0.
[43] Text modified as per modification 1 in integrated SAP, Version 3.0.

"treatment-emergent" data scope will be censored at the date of last double-blind dose of antithrombotic study treatment + 2 days.

Note that if a subject stops treatment at the Final rivaroxaban/aspirin Follow-up Visit and experiences an event up to 2 days thereafter, the event will be counted in this analysis but not in the primary analysis using the ITT data scope.

- For secondary safety analyses based on the safety analysis set and the "plus 30 days safety" data scope, all randomized subjects with at least one dose of study medication and without documentation of an outcome[44] event within the "plus 30 days safety" data scope will be censored at the date of last double-blind dose of antithrombotic study treatment + 30 days.

  Note that if a subject stops treatment at the Final rivaroxaban/aspirin Follow-up Visit and experiences an event up to 30 days thereafter, the event will be counted in this analysis but not in the primary analysis using the ITT data scope.

- For secondary safety analyses based on the safety analysis set and the "Study rivaroxaban/aspirin Follow up + Wash out" data scope, all randomized subjects with at least one dose of study medication and without documentation of an outcome[45] event will be censored at the subject's last contact date during the rivaroxaban/aspirin portion of the study.

Censoring rules for secondary safety analyses related to the pantoprazole/placebo randomization

- For "treatment-emergent" safety analyses, all randomized subjects with at least one dose of pantoprazole/placebo study medication and without documentation of an outcome[46] event within the "treatment-emergent" data scope will be censored at the date of last dose of pantoprazole study treatment + 2 days.
- For safety analyses based on the safety analysis set and the "Follow up + Wash out" data scope, all randomized subjects with at least one dose of pantoprazole/placebo study medication and without documentation of an outcome[47] event will be censored at the date of last trial contact.

[44] Text modified as per modification 1 in integrated SAP, Version 3.0.
[45] Text modified as per modification 1 in integrated SAP, Version 3.0.
[46] Text modified as per modification 1 in integrated SAP, Version 3.0.
[47] Text modified as per modification 1 in integrated SAP, Version 3.0.

5. Analysis Sets

5.1 Assignment of analysis sets

All subjects who have been randomized in the COMPASS study are valid for assignment to analysis sets.

5.1.1 Intention-to-Treat Analysis Set (ITT) - Amended

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all unique[48] randomized subjects.

If a subject is unintentionally randomized twice in the study, the subject will be included in the statistical analysis with the ID from the site where the initial randomization took place. Data from the randomization at the second site will be documented and reported[49].

5.1.2 Safety Analysis Set (SAF) - Amended[50]

The safety analysis set for secondary analyses related to the rivaroxaban/aspirin randomization will include all unique randomized subjects who received at least one dose of rivaroxaban/aspirin study medication.

The safety analysis set for secondary analyses related to the pantoprazole randomization will include all unique randomized subjects who received at least one dose of randomized pantoprazole/placebo medication.

6. Statistical Methodology

All data will be listed and all variables will be summarized by means of descriptive statistics according to their type.

Summaries by randomized antithrombotic study treatment group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. No imputation will be applied, unless specified otherwise in the SAP. Descriptive statistics such as mean, standard deviation, median, quartiles (inter quartile range), minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Life tables and Kaplan-Meier estimates will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data. Confidence intervals will be provided at a 2-sided level of 95% unless otherwise stated.

6.1 Population characteristics

Note that all summaries related to the pantoprazole randomization described in this section of the SAP will only be provided at the end of the pantoprazole portion of the study.

[48] Text added as per modification 4 in integrated SAP, Version 3.0.
[49] Text added as per modification 4 in integrated SAP, Version 3.0.
[50] Text modified as per modification 1 in integrated SAP, Version 4.1.

6.1.1 Disposition

The following will be tabulated overall and/or by antithrombotic treatment group:

- Study sample sizes by region and country
- Study sample sizes by country and site
- Subject disposition
- Number of subjects and primary reasons for screening failures
- Number of subjects and primary reasons for run-in phase failures
- Number of subjects eligible for pantoprazole randomization
- Number of subjects and primary reasons for premature permanent discontinuation of study medication (for each type of randomized study medication, as applicable regarding the portion of the study)
- Number of subjects and primary reasons for premature permanent discontinuation of study follow up

The number of subjects randomized after CABG surgery will be displayed.

Incidences for permanent discontinuation of the double-blinded antithrombotic study drug(s) and of the follow-up period will be provided by randomized antithrombotic study treatment groups, based on the case report form data. In addition, incidences for permanent discontinuation of the double-blinded pantoprazole study drug and of the follow-up period will be provided by pantoprazole treatment groups, including the group of subjects not considered eligible for pantoprazole randomization, based on the case report form data.

Kaplan-Meier estimates will be used to present

- time to the date of last double-blind dose of antithrombotic study treatment (calculated as days from randomization),
- time to the date of last double-blind dose of pantoprazole study treatment (after completion of pantoprazole/placebo portion of the study), and
- time to the date of last follow-up contact,

all calculated as days from randomization, by randomized (antithrombotic or pantoprazole) study treatment group.

Other details regarding visit adherence (e.g., visit completed in person, by telephone, through third party) and completion as well as study drug adherence collected via CRFs will be summarized using frequency tables by visit and randomized antithrombotic study treatment group.

6.1.2 Protocol Deviations

No per protocol analysis set will be defined in this study. The number of subjects with major protocol deviations according to the CRF will be summarized by randomized antithrombotic study treatment group. The types of deviations will be described in the Data Management Plan.

6.1.3 Medical and Surgical History

Medical history data will be evaluated by frequency tables, showing the number of subjects with medical history findings (i.e., listed conditions of previous diagnoses, diseases, or surgeries based on the CRF) that started before signing of the informed consent and that are considered relevant to the study.

For subjects randomized after CABG surgery, all characteristics of the CABG surgery collected on the corresponding randomization CRF page will be summarized.

6.1.4 Outcomes During Run-in Phase

The number of subjects with events since enrollment but before randomization (as reported on the Randomization CRF page) will be summarized by event type.

6.1.5 Demographics

Demographic data (obtained at the Screening Visit) will be evaluated descriptively for the ITT population as well as for the population for secondary safety analyses, by randomized antithrombotic study treatment groups, by proton pump inhibitor (PPI) study treatment groups, and overall.

Descriptive statistics (such as mean, standard deviation, median, quartiles (inter quartile range), minimum and maximum) will be provided for continuous variables such as

- Age [years]
- Height [cm]
- Weight [kg]
- Waist and hip circumference [cm]
- Body mass index [kg/m²]

Counts and (appropriate) percentages will be provided for categorical variables such as

- Gender
- Ethnic group and ethnicity/race
- Tobacco use

The number of subjects taking a proton pump inhibitor at baseline will be summarized by medication name.

For subjects randomized after CABG surgery, the pre-operative standard additive EuroSCORE (European System for Cardiac Operative Risk Evaluation) model will be applied. The EuroSCORE is a scoring system for the prediction of operative mortality for subjects undergoing cardiac surgery, where higher scores suggest a higher risk. The total score obtained will be summarized by descriptive statistics and frequency tables using the categories based on EuroSCORE classification (0-2, 3-4, 5+).

Furthermore, frequency tables will be used to summarize adherence prediction data obtained at the Screening / Run-in Visit.

Data on health care costs and driving status will be listed in the Appendix of the Clinical Study Report.

6.1.6 Other Baseline Characteristics

The number of subjects falling in the categories of the list of subgroup variables, see subsection 6.2.5, will be summarized by means of frequency tables, by both randomized antithrombotic and pantoprazole study treatment groups and overall. [51]

In addition, the number and proportion of subjects who

- prematurely discontinued randomized study treatment (by medication type)
- have been declared as lost to follow-up

will be summarized by the baseline characteristics listed above and study medication.

6.1.7 Prior and Concomitant Medication

Frequency tables will be used to summarize the number of subjects with

- prior relevant antiplatelet agents and anticoagulant reported by the subject at the Screening/Run-in Visit
- type of proton pump inhibitor reported by the subject at the Screening/Run-in Visit
- relevant concomitant medications at randomization (non-study medications taken regularly for at least 1 month at the time of the randomization visit): non-study proton pump inhibitor, ACE inhibitor/ Angiotensin receptor blocker (ARB), alpha blocker or other vasodilator, diuretic, lipid lowering agent, calcium channel blocker, beta blocker, Non-steroidal anti-inflammatory drugs (NSAIDs), hypoglycemic agent, selective serotonin reuptake inhibitors (SSRIs).
- non-study antithrombotic therapy (antiplatelet agents and anticoagulant) reported at the scheduled follow-up visits
- relevant concomitant medications recorded at a Follow-Up Visit 2 years after randomization
- relevant concomitant medications recorded at the Final rivaroxaban/aspirin Follow-Up Visit and the Final Follow-Up Visit.

Non-study medications reported on any of the event reports (e.g., angina, heart failure, AEs) will be displayed separately.

6.1.8 Extent of Study Follow-up and Exposure - Amended[52]

The total duration of study follow-up for a subject in the rivaroxaban/aspirin portion of the study and overall will be calculated as follows:

- Total duration of <rivaroxaban/aspirin, study> follow-up =
  Date of last <rivaroxaban/aspirin, study> follow-up contact – Randomization date + 1.

[51] Text modified as per modification 5 in integrated SAP, Version 3.0.
[52] Text modified as per modification 1 in integrated SAP, Version 4.1.

Total duration of antithrombotic study treatment will be calculated as follows:

- Total duration of antithrombotic study treatment (including days on/off study drug) =
  Date of last double-blind dose of antithrombotic study treatment –
  Randomization date + 1

For the different types of study medication, total treatment duration will be calculated as:

- Total duration of study treatment <type> (including days on/off study drug) =
  Date of last dose of study treatment <type> – Randomization date + 1,

  where <type> is replaced by rivaroxaban(/rivaroxaban placebo), aspirin(/aspirin placebo), and pantoprazole(/pantoprazole placebo).

Descriptive statistics for total duration of study follow-up and study treatment will be provided by treatment group.

Because the number of days off study drug cannot be reliably determined from the CRF data, no study duration excluding study drug interruptions or compliance will be calculated. However, the number and length of study drug interruptions and/or study drug dose reductions as far as documented on any CRF page will be summarized by means of descriptive statistics by randomized study treatments.

Frequency tables will be used to summarize compliance to study drug since last visit (i.e., at least 80% of pills taken) by visit and randomized study treatments.

6.2 Efficacy

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided type I error level of $\alpha = 0.05$ and all confidence intervals at a 2-sided level of 95%. Due to the conservative boundaries according to Haybittle – Peto used for interim analyses, no adjustment will be performed for the final primary efficacy analysis.

Primarily, for time-to-event analyses the censoring mechanism will be assumed to be non-informative due to an anticipated low non-cardiovascular death rate and almost complete follow-up for outcomes within this trial (according to expectations). Subjects will be handled as right-censored in primary time-to-event analyses. For the unexpected case that sensitivity analyses are needed, please refer to Section 6.2.7.

The trial success will be determined based on the totality of evidence for significance, magnitude, and direction of treatment effect from the analysis of primary and secondary efficacy outcomes. [53]

The recommendation by the independent DSMB to stop the rivaroxaban/aspirin arms early due to overwhelming efficacy after the first interim analysis was guided by a modified Haybittle-Peto rule, expecting “a reduction of at least 4 standard deviations in the analysis of the primary efficacy outcome”. The 2-sided type I error level corresponding to this decision rule can be calculated via $\alpha^* = \Phi(-4) + 1 - \Phi(4) = 0.0000633$, where Φ denotes the cumulative distribution function of the standard normal distribution. Considering the two comparisons, one for each rivaroxaban-treatment

[53] Text deleted as per integrated CSP, Version 3.0.

arm, being made according to this rule, the type I error level applied at the first interim analysis is about $\alpha_1 = 2\alpha^* = 0.0001267$. [54]

Testing strategy[55]

Each of the rivaroxaban-based treatment groups will first be compared to the common aspirin control group on the primary efficacy outcome, followed by the same comparisons on the three ordered secondary efficacy outcomes. Figure 6-1 illustrates the hypothesis testing problem with ordered hypotheses. The null hypotheses of no effect corresponding to different efficacy outcomes will be grouped into four separate families. Standard logical restrictions will be imposed, i.e., the null hypotheses will be split into two branches corresponding to the tests for rivaroxaban 2.5 mg plus aspirin (hypotheses H_{1A}, H_{2A}, H_{3A}, H_{4A}) and to the tests for rivaroxaban 5.0 mg (hypotheses H_{1B}, H_{2B}, H_{3B}, H_{4B}). A null hypothesis within each branch can be tested if and only if the immediately preceding null hypothesis is rejected, e.g., hypothesis H_{2A}, is "testable" if and only if hypothesis H_{1A} is rejected. In Figure 6-1, these logical restrictions are represented by arrows.

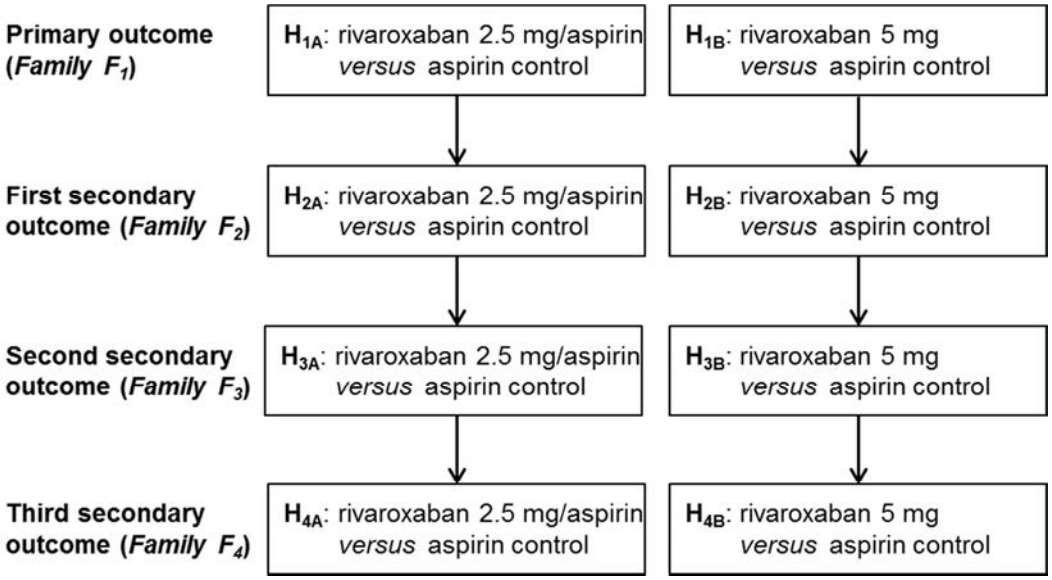

Figure 6-1: **Hypothesis testing problem**

Multiple hypotheses testing will be performed according to a mixture gatekeeping procedure based on the Hochberg test with a truncation fraction of $\gamma = 0.9$, which controls the familywise error rate at the pre-assigned level of significance $\alpha = 5\%$ in the strong sense. The Hochberg-based gatekeeping procedure based on an extension of the general mixture methodology developed in Dmitrienko and Tamhane (2011, 2013) (3, 4) was recently proposed in Brechenmacher et al., 2011 (1). It has found multiple applications in Phase III clinical trials. For example, it was successfully applied to construct powerful gatekeeping procedures in lurasidone Phase III clinical trials (Meltzer et al., 2011 [16]; Brechenmacher et al., 2011 [1]).

The Hochberg-based gatekeeping procedure provides strong Type I error rate control across the four families of null hypotheses. Key features of the Hochberg-based gatekeeping procedure include:

[54] Text modified as per modification 2 in integrated SAP, Version 4.1.
[55] Text added as per integrated CSP, Version 3.0.

- The gatekeeping procedure accounts for the logical restrictions defined above.
- The gatekeeping procedure utilizes powerful Hochberg-type tests for testing the hypotheses within each family:
  - Families 1 to 3: Truncated Hochberg test.
  - Family 4: Regular Hochberg test.

  Formal definitions of the regular and truncated Hochberg tests are given in Appendix 10.3.
- The gatekeeping procedure uses the truncated Hochberg test in Families 1 to 3 because the families serve as gatekeepers for the next family in the sequence. The regular Hochberg test is applied in Family 4 since this is the last family in the testing sequence. Thanks to the truncated Hochberg test, the gatekeeping procedure can pass a gatekeeper even if only one test is significant in this gatekeeper (for example, proceed to Family 2 if only one of the two rivaroxaban regimen is significantly different from aspirin control in Family 1). The truncated Hochberg tests in Families 1 to 3 are defined using a pre-specified truncation parameter γ, here $\gamma = 0.9$.

It is important to point out that the regular and truncated Hochberg tests control the local Type I error rate within each family of hypotheses. The test statistics within each family follow a bivariate normal distribution with a positive correlation and thus the positive dependence condition (MTP2 condition), which guarantees local familywise error rate control, is met (Sarkar and Chang, 1997 [18]; Sarkar, 1998 [19]). Further, the Hochberg-based gatekeeping procedure does not make any assumptions about the correlations across the four families of hypotheses.

In the following, a simple stepwise algorithm of the Hochberg-based gatekeeping procedure for the COMPASS study based on a truncation fraction of $\gamma = 0.9$ is described in detail. A truncation fraction γ close to 1 has been chosen to ensure a high probability of success for the primary hypotheses, considering that potentially only a small fraction of α is carried forward to the next family of hypotheses.

Step 1 (Family 1):
The two dose-placebo comparisons in Family 1 (Hypotheses H_{1A} and H_{1B}) will be performed using a truncated Hochberg test with the pre-specified truncation parameter $\gamma = 0.9$ at α=0.05. Consider the null hypotheses H_{1A} and H_{1B} and their associated raw p-values p_{1A} and p_{1B}.

(a) If $\max(p_{1A}, p_{1B}) \leq \alpha\,(1+\gamma)/2 = 0.0475$,
then reject both hypotheses H_{1A} and H_{1B} and continue with Step 2a.

(b) If $\max(p_{1A}, p_{1B}) > \alpha\,(1+\gamma)/2 = 0.0475$ and
$\min(p_{1A}, p_{1B}) \leq \alpha/2 = 0.025$,
then accept H_{ik}, for all i = 1,2,3,4 where k ϵ {A,B} corresponds to the hypothesis yielding the larger of the two p-values and reject H_{1j}, where j ϵ {A,B} corresponds to the hypothesis yielding the smaller of the two p-values and continue with Step 2b.

(c) If $\max(p_{1A}, p_{1B}) > \alpha\,(1+\gamma)/2 = 0.0475$ and

$\min(p_{1A}, p_{1B}) > \alpha/2 = 0.025$,
then accept H_{ik}, for all i = 1,2,3,4 and all k = A,B and stop.

Step 2 (Family 2):
The overall significance level used in Family 2 is determined by the number of significant tests in Step 1. If both null hypotheses H_{1A} and H_{1B} are rejected in Step 1, continue with Step 2a. If only one null hypothesis is rejected in Step 1, the corresponding null hypothesis will be tested according to Step 2b.

Step 2a:
The two dose-placebo comparisons in Family 2 (Hypotheses H_{2A} and H_{2B}) will be performed using a truncated Hochberg test with the pre-specified truncation parameter γ at the full α=0.05. Consider the null hypotheses H_{2A} and H_{2B} and their associated raw p-values p_{2A} and p_{2B}.

(a) If $\max(p_{2A}, p_{2B}) \leq \alpha (1+\gamma)/2 = 0.0475$,
then reject both hypotheses H_{2A} and H_{2B} and continue with Step 3a.

(b) If $\max(p_{2A}, p_{2B}) > \alpha (1+\gamma)/2 = 0.0475$ and
$\min(p_{2A}, p_{2B}) \leq \alpha/2 = 0.025$,
then accept H_{ik}, for all i =2,3,4, where $k \in \{A,B\}$ corresponds to the hypothesis yielding the larger of the two p-values and reject H_{2j}, where $j \in \{A,B\}$ corresponds to the hypothesis yielding the smaller of the two p-values and continue with Step 3b.

(c) If $\max(p_{2A}, p_{2B}) > \alpha (1+\gamma)/2 = 0.0475$ and
$\min(p_{2A}, p_{2B}) > \alpha/2 = 0.025$,
then accept H_{ik}, for all i = 2,3,4 and all k = A,B and stop.

Step 2b: Consider the null hypothesis H_{2j}, where $j \in \{A,B\}$ corresponds to null hypothesis H_{1j} rejected in step 1, and its associated raw p-value p_{2j}. Null hypothesis H_{2j} will be tested using the univariate test at $\alpha(1-\gamma)/2$.

(a) If $p_{2j} \leq \alpha(1-\gamma)/2 = 0.0025$,
then reject H_{2j} and continue with Step 3b.

(b) If $p_{2j} > \alpha(1-\gamma)/2 = 0.0025$,
then accept H_{ij}, for all i = 2,3,4 and stop.

Step 3 (Family 3):
The overall significance level used in Family 3 is determined by the number of significant tests in Steps 1 and 2. If all null hypotheses are rejected in Steps 1 and 2, continue with Step 3a.
If both null hypotheses are rejected in Step 1 and one null hypothesis is rejected in Step 2 or if one null hypothesis is rejected in Step 1 and one null hypothesis is rejected in Step 2, continue with Step 3b.

Step 3a: The two dose-placebo comparisons in Family 3 (Hypotheses H_{3A} and H_{3B}) will be performed using a truncated Hochberg test with the pre-specified truncation parameter γ at the full α=0.05. Consider the null hypotheses H_{3A} and H_{3B} and their associated raw p-values p_{3A} and p_{3B}.

(a) If $\max(p_{3A}, p_{3B}) \leq \alpha\,(1+\gamma)/2 = 0.0475$,
then reject both hypotheses H_{3A} and H_{3B} and continue with Step 4a.

(b) If $\max(p_{3A}, p_{3B}) > \alpha\,(1+\gamma)/2 = 0.0475$ and
$\min(p_{3A}, p_{3B}) \leq \alpha/2 = 0.025$,
then accept H_{ik}, for all i = 3,4 where k ϵ {A,B} corresponds to the hypothesis yielding the larger of the two p-values and reject H_{3j}, where j ϵ {A,B} corresponds to the hypothesis yielding the smaller of the two p-values and continue with Step 4b.

(c) If $\max(p_{3A}, p_{3B}) > \alpha\,(1+\gamma)/2 = 0.0475$ and
$\min(p_{3A}, p_{3B}) > \alpha/2 = 0.025$,
then accept H_{ik}, for all i = 3,4 and all k = A,B and stop.

Step 3b: Consider the null hypothesis H_{3j}, where j ϵ {A,B} corresponds to null hypothesis H_{2j} rejected in step 2, and its associated raw p-value p_{3j}. Null hypothesis H_{3j} will be tested using the univariate test at $\alpha(1-\gamma)/2$.

(a) If $p_{3j} \leq \alpha(1-\gamma)/2 = 0.0025$,
then reject H_{3j} and continue with Step 4b.

(b) If $p_{3j} > \alpha(1-\gamma)/2 = 0.0025$,
then accept H_{ij}, for all i = 3,4 and stop.

Step 4 (Family 4):
The overall significance level used in Family 4 is determined by the number of significant tests in Steps 1, 2, and 3. If all null hypotheses are rejected in Steps 1 to 3, continue with Step 4a. If both null hypotheses are rejected in Step 1 and 2 and one null hypothesis is rejected in Step 3 or if both null hypotheses are rejected in Step 1 and one null hypothesis is rejected in Steps 2 and 3 or if one null hypothesis is rejected in Steps 1 to 3, continue with Step 4b.

Step 4a: The two dose-placebo comparisons in Family 4 (Hypotheses H_{4A} and H_{4B}) will be performed using a regular Hochberg test at the full α=0.05. Consider the null hypotheses H_{4A} and H_{4B} and their associated raw p-values p_{4A} and p_{4B}.

(a) If $\max(p_{4A}, p_{4B}) \leq \alpha = 0.05$,
then reject both hypotheses H_{4A} and H_{4B}.

(b) If $\max(p_{4A}, p_{4B}) > \alpha = 0.05$ and
$\min(p_{4A}, p_{4B}) \leq \alpha/2 = 0.025$,
then accept H_{4k}, where k ϵ {A,B} corresponds to the hypothesis yielding the larger of the two p-values and reject H_{4j}, where j ϵ {A,B} corresponds to the hypothesis yielding the smaller of the two p-values.

(c) If $\max(p_{4A}, p_{4B}) > \alpha = 0.05$ and
$\min(p_{4A}, p_{4B}) > \alpha/2 = 0.025$,
then accept H_{4k}, for all k = A,B.

Step 4b: Consider the null hypothesis H_{4j}, where $j \in \{A,B\}$ corresponds to null hypothesis H_{3j} rejected in step 3, and its associated raw p-value p_{4j}. Null hypothesis H_{4j} will be tested using the univariate test at $\alpha(1-\gamma)/2$.

(a) If $p_{4j} \leq \alpha(1-\gamma)/2 = 0.0025$,
then reject H_{4j}.

(b) If $p_{4j} > \alpha(1-\gamma)/2 = 0.0025$,
then accept H_{4j}.

6.2.1 Primary Efficacy

6.2.1.1 Primary Efficacy Variable

The primary efficacy variable is the time (in days) from randomization to the first occurrence of the following primary efficacy outcome events:

- Myocardial infarction
- Stroke
- Cardiovascular death

All unrefuted[56] primary efficacy outcome events within the data scope according to intention-to-treat principle (see Section 4.5.2) will be considered for the derivation of the primary efficacy variable.

- For those subjects with documentation of an unrefuted[57] primary efficacy outcome event occurring

  after the date and time of randomization and up until the minimum (earliest) of the global rivaroxaban/aspirin outcomes cut-off date and the subject's last contact date during the rivaroxaban/aspirin portion of the study[58]

  time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:

  - the date of the subject's first primary efficacy outcome event – the randomization date + 1.

  This will constitute an uncensored observation.

- For those subjects without documentation of an unrefuted[59] primary efficacy outcome event within the data scope according to intention-to-treat principle,
  time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:

[56] Text modified as per modification 1 in integrated SAP, Version 3.0.
[57] Text modified as per modification 1 in integrated SAP, Version 3.0.
[58] Text modified as per modification 1 in integrated SAP, Version 4.1.
[59] Text modified as per modification 1 in integrated SAP, Version 3.0.

- the minimum (earliest) of {the global rivaroxaban/aspirin outcomes cut-off date, the subject's last contact date during the rivaroxaban/aspirin portion of the study} – the randomization date +1.[60]

This will constitute a right-censored observation.

6.2.1.2 Primary Efficacy Analysis

Analysis of the primary efficacy outcome will be based on the intention-to-treat principle. Two comparisons will be performed to compare each of the rivaroxaban-based treatment groups to the common aspirin-control group to evaluate:

- Superiority of rivaroxaban 2.5 mg bid + aspirin 100 mg od over rivaroxaban placebo + aspirin 100 mg od (control)
- Superiority of rivaroxaban 5 mg bid + aspirin placebo over rivaroxaban placebo + aspirin 100 mg od (control).

The primary null hypothesis $H_{0;riva2.5}$:

"There is no difference between
the rivaroxaban 2.5 mg bid + aspirin 100 mg od treatment group and
the rivaroxaban placebo + aspirin 100 mg od (control)
in the probability of the primary efficacy outcome
for all time points $t \geq 0$ relative to randomization."

will be tested against the alternative hypotheses $H_{1;riva2.5}$:

"There is a difference between
the rivaroxaban 2.5 mg bid + aspirin 100 mg od treatment group and
the rivaroxaban placebo + aspirin 100 mg od (control)
in the probability of the primary efficacy outcome
for at least one time point $t \geq 0$ relative to randomization."

The corresponding primary null hypothesis $H_{0;riva5}$ will be tested comparing rivaroxaban 5 mg bid + aspirin placebo treatment with rivaroxaban placebo + aspirin 100 mg od (control). Statistical testing will be performed by a comparison of the "survival functions" $S(t)$, i.e., the probability that "time from randomization to the first occurrence of the following primary efficacy outcomes" is $> t$, for a time t relative to randomization.

The 2 comparisons will be performed using two separate stratified log-rank tests. Proton pump inhibitor use (3 strata levels: not randomized to a proton pump inhibitor; pantoprazole 40 mg od; pantoprazole placebo) will be used as a stratification factor in the statistical analysis. Study center will not be used as a stratification factor in the statistical analysis.

Following the mixture gatekeeping procedure as mentioned in Section 6.2, a truncated Hochberg test with the pre-specified truncation parameter $\gamma = 0.9$ at $\alpha=0.05$ will be used.

There will be no formal comparison between the rivaroxaban 2.5 mg bid + aspirin 100 mg od and rivaroxaban 5 mg bid + aspirin placebo groups.

[60] Text modified as per modification 1 in integrated SAP, Version 4.1.

Kaplan-Meier estimates of cumulative risk functions and Nelson-Aalen estimates of the cumulative hazard functions will be provided to evaluate the timing of event occurrence in the 3 antithrombotic study groups and the consistency of the respective treatment effects for all time points (the two survival curves in each comparison do not cross).

To derive the log-rank Z test statistic and the variance V of the log-rank statistics, SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.05 METHOD=KM NELSON;
  STRATA stratumn / GROUP=trtgrpn TEST=(LOGRANK);[61]
  TIME ttevalue * ttecnsr(0);
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
stratumn = variable for PPI stratification factor (three levels)
*/
```

Hazard ratio, relative risk reduction (RRR; RRR = 100 × [1 – hazard ratio]%), and corresponding 2-sided 95% confidence intervals will be estimated based on two separate stratified Cox proportional hazards models. Censoring will be assumed independent of the randomized group assignment.

For the analysis of the primary outcome in this study, the hazard function h(t) is the chance that an individual experiences an event of the primary efficacy outcome in the next instant in time, given that the individual has not had such an event up to time t. For example, for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od with rivaroxaban placebo + aspirin 100 mg od (control), the corresponding stratified Cox proportional hazards model can be described by the following equation:

$$h_k(t,x_i) = h_{0k}(t) \exp(\beta x_i),$$

where

$h_k(.)$ hazard function for primary efficacy outcome for stratum k, k = 1,2,3 (k represents PPI stratification factor), as a function of time and subject's covariates

$h_{0k}(.)$ unspecified underlying baseline hazard function for primary efficacy outcome per stratum k; hazard of an individual with $x_i = 0$

t time (in days) relative to the randomization date

[61] Text modified as per modification 3 in integrated SAP, Version 4.1.

x_i antithrombotic treatment group of subject i
(0 corresponds to "rivaroxaban placebo + aspirin 100 mg od (control)" and
1 corresponds to "rivaroxaban 2.5 mg bid + aspirin 100 mg od")

β unknown parameter (to be estimated); hazard ratio = exp(β)

SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
stratumn = variable for PPI stratification factor (three levels)
*/
```

Additional procedure options controlling the output may be added to the program codes.

Sensitivity analyses[62]

Sensitivity analyses will be performed to include all primary efficacy outcome events up until the minimum (earliest) of the Final rivaroxaban/aspirin Follow-up Visit date and the subject's last contact date during the rivaroxaban/aspirin portion of the study.

In addition, the number of primary efficacy outcome events occurring after the Final rivaroxaban/aspirin Follow-up Visit until the rivaroxaban/aspirin Washout Telephone Visit, included in the clean database for the rivaroxaban/aspirin comparisons, will be summarized by rivaroxaban/aspirin study treatment group.

The plausibility of the proportional hazards assumption will be assessed by visually examining both the plot of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log time for evidence of non-parallelism and the smoothed plot of the scaled Schoenfeld residuals to directly visualize the log hazard ratio (Grambsch and Therneau, 1994 [8]), for each stratum separately, and by including a time-treatment interaction term in the Cox model (time log transformed). The SAS code is adapted as follows:

[62] Text modified as per modification 1 in integrated SAP, Version 4.1.

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn trtltime / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
  trtltime = trtgrpn*log(ttevalue);
RUN;
```

The significance of the interaction will be tested at the 5% type I error level. If the interaction is significant and there is strong evidence of non-proportionality from the plots, time-dependent hazard ratios will be estimated with the model that includes the interaction term.

Analysis of the joint effect and/or interaction of study treatments[63]

In addition, an analysis of the joint effect and/or interaction between rivaroxaban-based anti-thrombotic therapy and proton pump inhibitor use on the primary efficacy outcome will be performed for those subjects randomized to both antithrombotic and pantoprazole study medication. Joint effect and interaction between the antithrombotic and pantoprazole study groups on the primary efficacy outcome will be explored based on the intention-to-treat principle. The analysis will use two separate Cox proportional hazards models, one for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od, and one for the comparison of rivaroxaban 5 mg bid+ aspirin placebo vs. rivaroxaban placebo + aspirin 100 mg od.

The Cox proportional hazards model (e.g., for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od) can be described by the following equation:

$$h(t,x_{1i},x_{2i},x_{3i}) = h_0(t) \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_{12} x_{1i} x_{2i}),$$

where

$h(.)$ hazard function for primary efficacy outcome as a function of time and subject's covariates

$h_0(.)$ unspecified underlying baseline hazard function for primary efficacy outcome

t time (in days) relative to the randomization date

x_{1i} antithrombotic treatment group of subject i
(0 corresponds to "rivaroxaban placebo + aspirin 100 mg od (control)" and
1 corresponds to "rivaroxaban 2.5 mg bid + aspirin 100 mg od")

x_{2i} indicator variable for "pantoprazole 40 mg od treatment group",
i.e., $x_{2i} = 1$ if subject i was randomized to pantoprazole 40 mg treatment,
$x_{2i} = 0$ if subject i was randomized to pantoprazole placebo

$\beta_1, \beta_2, \beta_{12}$ unknown parameters (to be estimated)

SAS program code corresponding to the following will be used:

[63] Text added as per modification 7 in integrated SAP, Version 3.0.

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn ppigrpn trtgrpn*ppigrpn
                                / RL TIES=EFRON ALPHA=0.05;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ppigrpn = indicator variable: ppi1grpn = 1, if subject randomized to
           pantoprazole 40 mg treatment, else ppi1grpn = 0,
           if subject randomized to pantoprazole placebo
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
*/
```

If the interaction term for the two randomized treatments is significant at the 5% type I error level, then an interaction ratio will be calculated (McAlister et al., 2003 [15]) to describe the clinical significance of any synergy and sub-additivity of the two treatment effects on the primary efficacy outcome. For the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od this means that the following two ratios are determined, where the cumulative event rate is determined including all events considered in the primary analysis.

- Ratio A:
  Cumulative event rate for the primary efficacy outcome for subjects randomized to both rivaroxaban 2.5 mg bid + aspirin 100 mg od and pantoprazole 40 mg od divided by cumulative event rate for the primary efficacy outcome for subjects randomized to both rivaroxaban placebo + aspirin 100 mg od and pantoprazole 40 mg od
- Ratio B:
  Cumulative event rate for the primary efficacy outcome for subjects randomized to both rivaroxaban 2.5 mg bid + aspirin 100 mg od and pantoprazole placebo divided by cumulative event rate for the primary efficacy outcome for subjects randomized to both rivaroxaban placebo + aspirin 100 mg od and pantoprazole placebo.

The ratio of ratio A and ratio B gives an estimate of the interaction ratio. Given the large sample size of this trial, a very small interaction may be detected that lacks clinical significance. An interaction ratio estimate of ≤ 0.8 (antagonism or sub-additivity) or ≥ 1.25 (synergy) will be considered "clinically significant".

6.2.2 Secondary Efficacy

6.2.2.1 Secondary Efficacy Variables

Secondary efficacy variables are the time (in days) from randomization to the first occurrence of the following secondary efficacy outcomes[64] – in the order as specified below:

1. The composite of outcomes --- coronary heart disease death, myocardial infarction, ischemic stroke, acute limb ischemia
2. The composite of outcomes --- cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia
3. Mortality (all-cause)

The time-to-event variables will be derived similar to the derivation described in Section 6.2.1.1 for the primary efficacy variable.

In addition, a net clinical benefit time-to-event variable will be defined which is a composite of the

- primary efficacy outcome
- primary safety outcome, excluding bleedings leading to hospitalization and bleedings into surgical site associated with re-operation.[65]

6.2.2.2 Secondary Efficacy Analysis

Analysis of the secondary efficacy outcomes will be based on the intention-to-treat principle and will essentially use the same statistical methods, as described in Section 6.2.1.2. Both comparisons of the rivaroxaban-based treatment groups to the common aspirin-control group will be performed using the truncated and/or regular Hochberg tests as described in in Section 6.2 to control the family-wise error rate of 5%.[66]

6.2.3 Tertiary Efficacy

6.2.3.1 Tertiary Efficacy Variables

Tertiary efficacy variables are

- the time (in days) from randomization to the first occurrence of the following tertiary efficacy outcomes[67]:
    - Individual components of the primary and secondary outcomes, i.e., myocardial infarction, stroke, ischemic stroke, cardiovascular death, coronary heart disease death, acute limb ischemia, and all-cause mortality
    - Hospitalization for cardiovascular reasons
    - Hospitalization

[64] Text modified as per integrated CSP, Version 3.0.
[65] Text added as per modification 7 of the SAP, Version 4.0.
[66] Text modified as per integrated CSP, Version 3.0.
[67] Text modified as per integrated CSPs, Versions 2.0 and 3.0.

  - Venous thromboembolism
  - Revascularization
  - Amputation
  - Stent thrombosis
  - Unstable angina
  - Worsening angina
  - New angina
  - Heart failure
  - Resuscitated cardiac arrest
  - New diagnosis (/recurrence) of cancer
  - Coronary artery bypass graft failure
- Subject-reported SAGE, MoCA, DSS, and EQ-5D
- Medical resource utilization (MRU)

The time-to-event variables will be derived similar to the derivation described in Section 6.2.1.1 for the primary efficacy variable.

SAGE
The SAGE questionnaire comprises 15 items, each describing an activity for which the respondent has to indicate how much difficulty the subject has encountered in performing this activity in the past month. Regarding scoring for an item, 0 points are assigned if the participants endorse the "None/never performed" response, 1 point to the "Mild" response, 2 points to the "Moderate" response, and 3 points to the "Severe" response. One additional point will be assigned when in response to question 11, 12, and 15 the respondent declares the need for help from another person or a tool to walk, jump the stairs or to bath. The total score will range from 0, describing a very independent participant over a broad spectrum of activities, to 48, describing a very dependent subject.

MoCA
The Montreal Cognitive Assessment (MoCA) test assesses several cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. For each task correctly completed, one point is assigned. All subscores are summed up and adjusted for individuals with ≤ 12 years education to derive a total score ranging between 0 (for a totally cognitive impaired subject) and a maximum of 30 points (cognitively healthy participant).

DSS
The DSS test is a neuropsychological test sensitive to brain damage, dementia, age and depression. It consists of nine digit-symbol pairs followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (120 sec) is measured.

EQ-5D
EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Assessments will be done using both a descriptive system and the subject's self-rated health on a visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'.

The descriptive system comprises five dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety/depression). The subject is asked to indicate his/her current health state by ticking the most appropriate of three statements about each of the dimensions. Each statement has an increasing degree of severity (no problems / some problems / extreme problems) thus defining 243 health states.

Data from the EuroQoL questionnaire will be analyzed as available, no imputation of missing values will be performed. In case a subject ticks more than one level as responses for the same item, the item is set to missing.

The following variables are of interest:

- EQ-5D single dimensions
- EQ-5D index score, combining the recordings for each of the five EQ-5D dimensions into one single score (see Appendix 10.2)
- EQ-5D Visual Analogue Scale (VAS) values

6.2.3.2 Tertiary Efficacy Analysis

Analysis of the tertiary efficacy outcomes will be based on the intention-to-treat principle. The analysis of the time-to-event variables will be based on a similar approach as described in Section 6.2.1.2, including stratified log-rank tests, stratified Cox models, and Kaplan-Meier estimates. Both comparisons of the rivaroxaban-based treatment groups to the common aspirin-control group will be performed at the 2-sided 5% type I error level. There will be no adjustment of these analyses for multiple testing.

Subject reported data from the EQ-5D questionnaire will be summarized by means of descriptive statistics and frequency tables by antithrombotic treatment group and overall and by visit. All data will be listed in the Appendix of the Clinical Study Report. In depth analyses of the SAGE, MoCA, and DSS questionnaire data will be displayed in a separate report/after completion of the pantoprazole/placebo portion of the study. Additional analyses of the EQ-5D will be used for economic modeling. These analyses will be described in a separate SAP.

The analysis of MRU data will be described in a separate SAP. MRU data will be incorporated into economic modeling, which will be performed and reported separately from this study in a stand-alone report. The data will be listed in Appendix of the Clinical Study Report.

6.2.4 Analysis for Pantoprazole Randomization - Amended[68]

All analyses related to the pantoprazole randomization described in this section of the SAP will only be performed at the end of the pantoprazole portion of the study. The CSR related to the rivaroxaban/aspirin randomization will only use the pantoprazole/placebo randomization data for stratified testing and interaction analyses of efficacy / safety outcomes in relation to the rivaroxaban/aspirin randomization.

6.2.4.1 Variables for Pantoprazole Randomization - Amended[69]

The main variable for the pantoprazole randomization is the time (in days) from randomization to the first occurrence of the following outcomes:

- Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
- Overt upper gastrointestinal bleeding of unknown origin
- Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL[70]
- Symptomatic gastroduodenal ulcer
- Gastrointestinal pain with underlying multiple gastroduodenal erosions, obstruction or perforation

The time-to-event variable will be derived in a similar manner as originally described for the primary efficacy variable.

- For those subjects with documentation of an unrefuted pantoprazole outcome event occurring

  (a) after the date and time of randomization and up until the Final Follow-up Visit, or
  (b) after the date and time of randomization and up until the common trial close-out date, if the subject was not available for a Final Follow-up Visit up to the common trial close-out date

  time (in days) from randomization to the first occurrence of the unrefuted pantoprazole outcome will be derived as:

  - the date of the subject's first unrefuted pantoprazole outcome event – the randomization date + 1.

  This will constitute an uncensored observation.

- For those subjects without documentation of an unrefuted pantoprazole outcome event within the data scope according to intention-to-treat principle,
  time (in days) from randomization to the first occurrence of a pantoprazole outcome will be derived as:

[68] Text modified as per modification 1 in integrated SAP, Version 4.1.
[69] Text modified as per modification 6 in integrated SAP, Version 3.0.
[70] Text modified as per integrated CSP, Version 2.0.

- the subject's Final Follow-Up Visit date – the randomization date +1, if the subject was available for the Final Follow-Up Visit before the common trial close-out date.
- the subject's date of last follow-up contact up to the common trial close-out date – the randomization date +1, if
  (a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and
  (b) the subject's date of last trial contact is not after the common trial close-out date.
- the common trial close-out date – the randomization date +1, if
  (a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and
  (b) the subject's date of last trial contact is after the common trial close-out date.

This will constitute a right-censored observation.

Other outcomes of interest for the pantoprazole randomization are:

- pneumonia, enteric infections, and bone fractures as well as new diagnosis of gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, and dementia since randomization.

6.2.4.2 Statistical Analysis for Pantoprazole Randomization

The statistical analysis of the outcome for pantoprazole randomization will be based on the intention-to-treat principle and will include all subjects randomized to receive pantoprazole 40 mg od or pantoprazole placebo. The randomized pantoprazole 40 mg od study treatment group and randomized pantoprazole placebo-control group will be compared.

The null hypothesis $H_{0;panto40}$ stating that

"there is no difference between the pantoprazole treatment and control groups in the probability of the outcome for pantoprazole randomization for all time points" will be tested against the alternative hypothesis $H_{1;panto40}$ stating that

"there is a difference between the two groups in the probability of the outcome for at least one time point".

The comparison will be performed using a log-rank test stratified by antithrombotic study treatment (three strata levels: rivaroxaban 2.5 mg bid + aspirin 100 mg od; rivaroxaban 5 mg bid + aspirin placebo; rivaroxaban placebo + aspirin 100 mg od), conducted at the 2-sided 5% type I error level. There will be no interim analyses for the pantoprazole randomization.

Kaplan-Meier estimates of cumulative risk functions and Nelson-Aalen estimates of the cumulative hazard functions will be provided to evaluate the timing of event occurrence in the two proton pump inhibitor study groups and the consistency of the treatment effect for all time points (the two survival curves do not cross).

Hazard ratios, relative risk reduction, and corresponding 2-sided 95% confidence intervals will be estimated based on a Cox proportional hazards model stratified by antithrombotic therapy study group. Censoring will be assumed independent of the treatment group assignment. Similar

strategies to those outlined in Section 6.2.1.2 will be used for assessing the plausibility of the proportional hazards assumption.

For the analysis of the outcome for the pantoprazole randomization in this study, the hazard function h(t) is the chance that an individual experiences an event of the outcome of the pantoprazole randomization in the next instant in time, given that the individual has not had such an event up to time t. For example, for the comparison of pantoprazole 40 mg od to pantoprazole placebo (control), the corresponding stratified Cox proportional hazards model can be described by the following equation:

$$h_k(t,x_i) = h_{0k}(t) \exp(\beta x_i),$$

where

$h_k(.)$ hazard function for primary efficacy outcome for stratum k, k = 1,2,3 (k represents randomized antithrombotic study treatment stratification factor), as a function of time and subject's covariates

$h_{0k}(.)$ unspecified underlying baseline hazard function for primary efficacy outcome per stratum k; hazard of an individual with $x_i = 0$

t time (in days) relative to the randomization date

x_i PPI treatment group of subject i (0 corresponds to "pantoprazole placebo (control)" and 1 corresponds to "pantoprazole 40 mg od")

β unknown parameter (to be estimated); hazard ratio = $\exp(\beta)$

SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = ppi1grpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           pantoprazole 40 mg or pantoprazole placebo study treatment
ppi1grpn  = variable coding randomized pantoprazole treatment group
           (0 = pantoprazole placebo, 1 = pantoprazole 40 mg treatment)
ttevalue = time to first occurrence of pantoprazole outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
stratumn = variable for randomized antithrombotic study treatment
           stratification factor (three levels)
*/
```

Additional procedure options controlling the output may be added to the program codes.

In addition, joint effect and interaction between the antithrombotic and pantoprazole study groups on the pantoprazole outcome will be explored based on the intention-to-treat principle in subjects

randomized to receive pantoprazole 40 mg od or pantoprazole placebo. The analysis will use two separate Cox proportional hazards models, one for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od, and one for the comparison of rivaroxaban 5 mg bid+ aspirin placebo vs. rivaroxaban placebo + aspirin 100 mg od. The models will include:

- a covariate for the effect of the considered rivaroxaban-based treatment group vs. the aspirin-control group,
- a covariate for the effect of pantoprazole 40 mg od treatment group vs. pantoprazole placebo-control group,
- an interaction term of these two factors.

Therefore, the Cox proportional hazards model (e.g., for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od) can be described by the following equation:

$$h(t,x_{1i},x_{2i}) = h_0(t) \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_{12} x_{1i} x_{2i}),$$

where

$h(.)$ hazard function for pantoprazole outcome as a function of time and subject's covariates

$h_0(.)$ unspecified underlying baseline hazard function for pantoprazole outcome

t time (in days) relative to the randomization date

x_{1i} antithrombotic treatment group of subject i
(0 corresponds to "rivaroxaban placebo + aspirin 100 mg od (control)" and
1 corresponds to "rivaroxaban 2.5 mg bid + aspirin 100 mg od")

x_{2i} pantoprazole group of subject i
(0 corresponds to "pantoprazole placebo-control group" and
1 corresponds to "pantoprazole 40 mg od treatment group")

$\beta_1, \beta_2, \beta_{12}$ unknown parameters (to be estimated)

SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn ppi1grpn trtgrpn*ppi1grpn /
                                RL TIES=EFRON ALPHA=0.05;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ppi1grpn = variable coding randomized pantoprazole treatment group
           (0 = pantoprazole placebo, 1 = pantoprazole 40 mg treatment)
ttevalue = time to first occurrence of pantoprazole outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
*/
```

If the interaction term is significant at the 5% type I error level, then an interaction ratio will be calculated (McAlister et al., 2003 [15]) to describe the clinical significance of any synergy and sub-additivity of the two treatment effects on the pantoprazole outcome (see Section 6.2.1.2).

Additional exploratory analyses will include, e.g., a comparison of subjects who used proton pump inhibitor at baseline (and therefore were not randomized to receive pantoprazole 40 mg od or pantoprazole placebo) with subjects randomized to pantoprazole placebo group with regard to the pantoprazole outcome.

Further details characterizing gastrointestinal bleeding events collected on the Gastrointestinal CRF Report will be summarized by means of descriptive statistics and frequency tables.

6.2.5 Efficacy Subgroup Analysis - Amended[71]

Subgroup analyses

- for the primary efficacy outcome comparing
  - rivaroxaban 2.5 mg + aspirin with rivaroxaban placebo + aspirin 100 mg
  - rivaroxaban 5 mg + aspirin placebo with rivaroxaban placebo + aspirin 100 mg
- and for the outcome for pantoprazole randomization comparing
  - pantoprazole 40 mg with pantoprazole placebo

will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes. The subgroup analyses for the rivaroxaban/aspirin comparisons will be performed after the end of the study rivaroxaban/aspirin portion of the trial, while subgroup analyses for the pantoprazole comparison will be performed after the end of the pantoprazole portion of the trial. [72]

[71] Text modified as per modification 5 in integrated SAP, Version 3.0.
[72] Text modified as per modification 1 in integrated SAP, Version 4.1.

Homogeneity of treatment effect (i.e., the effect of antithrombotic study treatment on the primary efficacy outcome and effect of pantoprazole study treatment on the pantoprazole outcome) will be examined for the following subgroup variables, where important subgroups are distinguished from "other" subgroups that are examined to assess the consistency of a treatment effect:

Important subgroups

- Coronary artery disease (yes, no)
- Peripheral artery disease (yes, no)
- CAD and PAD (yes, no)
- CAD only, PAD only, CAD and PAD
- History of prior asymptomatic carotid artery stenosis >= 50%/revascularization (yes, no)
- History of polyvascular disease with number of vascular beds affected [CAD, PAD, cerebrovascular disease, i.e., prior stroke or asymptomatic carotid artery stenosis >= 50%/revascularization] (1, 2, or 3 vascular beds affected)
- Prior CABG surgery
    - Any prior CABG surgery (yes, no)
    - Study baseline CABG surgery [planned within 4-7 days before randomization] (yes, no)
    - Prior CABG surgery (no prior CABG surgery, study baseline CABG surgery, other history of prior CABG[73] surgery)
- CAPRIE-like population with medical history of any of the following prior events: MI, (ischemic) stroke, or PAD (yes, no)
- History of prior MI (yes, no)
- History of both prior MI and polyvascular disease or multivessel CAD (yes, no)

Other subgroups

- Region
    - North America, Western Europe and AUS/ISR/ZAF, Eastern Europe, Asia Pacific, and South America, see Appendix 10.1
    - US, non-US
- Sex (male, female)
- Age
    - Categories 1: <55, 55 to <65, 65 to 75, >75 years
    - Categories 2: < 65, ≥ 65 to < 75, ≥ 75 years
- Race (White or Caucasian, Black or African American, Asian, other)
- Body weight at baseline (≤ 60 kg, > 60 kg)
- Baseline renal function
    - estimated glomerular filtration rate (eGFR) categories 1: <60, ≥60 mL/min

[73] Bullet was added as per integrated CSP, Version 3.0.

  - eGFR categories 2: < 15, 15 to < 30, 30 to < 60, ≥ 60 mL/min
  - eGFR categories 3: < 30, 30 to 50, >50 to 80 ml/min, >80 ml/min
- Smoking status
  - Tobacco use at baseline (yes, no)
  - History of tobacco use (yes, no)
- Baseline proton pump inhibitor use (yes, no)
- Baseline lipid lowering agent use (yes, no)
- Baseline diabetes (yes, no)
- History of a prior heart failure (yes, no)
- History of peptic ulcer (yes, no)
- History of (non-lacunar ischemic) stroke (yes, no)
- History of peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty (yes, no)
- History of limb or foot amputation for arterial vascular disease (yes, no)
- History of hypertension (yes, no)
- History of prior coronary PTCA/Atherectomy/PCI (yes, no)
- History of prior MI and age < 65 years (yes, no)
- History of prior MI and reduced renal function, i.e., eGFR <60 mL/min (yes, no)

Additional subgroup analyses, if identified, will be specified before unblinding of treatment assignment. The pre-specified categories may be collapsed if the number of events is too small for some subgroups. In addition to analyses of the subgroups listed above, analyses for the Asian populations, especially Chinese and Japanese subjects, will be performed as required and presented in separate reports.

Homogeneity of study treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective stratified Cox proportional hazards model used in the main analysis. Cox proportional hazards regression model (not stratified) will be used for the subgroup variable referring to baseline proton pump inhibitor use (yes, no).

As the number of subgroup analyses may be large, the probability of observing at least one statistically significant but spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus any significant interactions in the analysis of primary outcomes will be interpreted as “flags” to prompt further investigation.

No interactions with any of the subgroup variables are expected. If,

- for important subgroups: the interaction term is significant at the 5% type I error level in the analysis of the primary efficacy outcome,
- for other subgroups: the interaction term is significant at the 1% type I error level in the analysis of the primary efficacy outcome and there is a biologically coherent explanation for the finding,

secondary and tertiary efficacy outcomes will be investigated to evaluate the plausibility of such an effect. Furthermore, in the analysis of all outcomes, if the interaction term is significant at the 5% type I error level, the likelihood ratio test proposed by Gail and Simon (1985) [7] will be performed to test the hypothesis that there is no crossover or qualitative interaction at the 1% type I error level (H_0: The direction of treatment effect is the same for all levels of a subgroup variable vs. H_1: The direction of treatment effect is different for at least one level of a subgroup variable). As was shown by Li et al (2007) [12], the probability of observing the treatment effect in the opposite direction to the true overall treatment effect for at least one subgroup level is not negligible. The contributing factors may be small subgroup sizes, imbalance of randomized groups within the subgroups, and small true overall treatment effect.

Following the test of interaction, hazard ratios (and relative risk reduction) with 2-sided 95% confidence intervals for the treatment effect will be estimated separately within each level of a subgroup variable using the stratified Cox proportional hazards models that were used in the main analyses of study outcomes.

In the subgroup of subjects randomized 4-7 days (according to protocol plan) after CABG surgery, further subgroup analyses as outlined above will be performed to investigate the consistency of the antithrombotic treatment effect across EuroSCORE categories (0-2, 3-4, 5+) on the primary efficacy outcome.

6.2.6 Analyses of the COMPASS MIND Substudy

Subclinical (i.e., covert) strokes are more frequent than clinically evident brain infarcts, with a prevalence of covert strokes of 15% to 20% in population-based cohorts with a mean age of 65 years.

The COMPASS MIND substudy is a magnetic resonance imaging (MRI) substudy evaluating the incidence of clinically silent brain infarcts and subclinical brain ischemia and the effect of the antithrombotic therapies being tested in COMPASS on covert cerebral ischemia, thereby providing additional information about mechanisms of disease and treatment benefits.

A total of 1,500 COMPASS participants will be invited to participate (500 subjects per treatment group, balanced for age, prior stroke, and hypertension). Participants will undergo limited brain MRI sequences at entry and near study end. Two-stage central interpretation blinded to treatment will be carried out, with all incident covert infarcts confirmed by a second independent interpreter. Subjects will have DNA collected at baseline and blood collected at baseline and at the 1 month visit.

Data related to the COMPASS MIND substudy will be reported separately.[74]

6.2.6.1 Variables of the COMPASS MIND Substudy

Outcomes of the COMPASS MIND substudy are:

- Covert brain infarcts
  (detected by blinded comparison of initial vs. end-study MRIs)

[74] Text modified as per modification 1 in integrated SAP, Version 4.1.

- Non-lacunar covert brain infarcts
- All incident strokes, including clinical strokes and all covert strokes

Furthermore, functional decline (based on SAGE), cognitive decline (based on MoCA and DSS), and biomarkers (C-reactive protein, NT-proBNP) will be assessed.

6.2.6.2 Statistical Analysis of the COMPASS MIND Substudy

The incidence of the COMPASS MIND substudy outcomes will be determined for each antithrombotic study treatment group. Two comparisons will be performed to compare

- rivaroxaban 2.5 mg bid + aspirin 100 mg od treatment with rivaroxaban placebo + aspirin 100 mg od (control), and
- rivaroxaban 5 mg bid + aspirin placebo treatment with rivaroxaban placebo + aspirin 100 mg od (control)

within the subpopulation included in the COMPASS MIND substudy.

Functional and cognitive decline as well as the predictive value of biomarkers as independent predictors of covert brain infarcts will be explored by means of descriptive statistics. Details of additional analyses will be described in a separate document; results will be reported separately.

6.2.7 Exploratory Analyses

In the unexpected event that the number of subjects who need to be declared as lost to follow-up is unexpectedly high and evidence suggests that the assumption of non-informative censoring cannot be adopted, additional sensitivity analyses might be performed in order to evaluate the robustness of the primary analysis. Where a subject is completely non-compliant with study follow up, the likelihood that this participant has experienced a study outcome will be derived and this information incorporated, as appropriate, in the analyses (Little et al., 2012 [13]). With SAP amendment v3.0, integrated in SAP, Version 4.0, sensitivity analyses to address the potential impact of missing data on the results of the primary analysis are described in Appendix 10.4.[75]

The types of myocardial infarction and further details obtained on the myocardial infarction (MI) CRF Reports will be summarized at the event level by randomized antithrombotic study treatment group for subjects who experienced MI events during the study. The efficacy outcomes will also be evaluated by MI types according to the universal definition, see derivation document for details.[76]

Symptoms, recovery status (Rankin scale), and further details obtained on the Stroke CRF Reports will be summarized at the event level by randomized antithrombotic treatment group for subjects who experienced ‘stroke’ events during the study.

Further characteristics related to heart failure obtained on the Heart Failure CRF Reports will be summarized at the event level by randomized antithrombotic treatment group for subjects who experienced ‘heart failure’ events during the study.

[75] Text added as per modification 4 in integrated SAP, Version 4.1.
[76] Text added as per modification 8 in integrated SAP, Version 3.0.

Further characteristics related to venous thromboembolisms obtained on the VTE CRF Reports will be summarized at the event level by randomized antithrombotic treatment group for subjects who experienced 'venous thromboembolisms' events during the study.

Further characteristics related to new diagnoses (/recurrence) of cancer obtained on the Cancer CRF Reports will be summarized at the event level by randomized antithrombotic treatment group for subjects who experienced 'new diagnoses of cancer' events during the study.

If applicable, information on subjects with multiple outcome events will be displayed as appropriate. Further tables summarizing study data will be specified in the TLF document.

Efficacy events occurring after the discontinuation of antithrombotic study treatment will be summarized for the subjects who have at least 1 day follow-up post last dose of antithrombotic study medication by treatment group and summarized by means of frequency tables. Specifically, events occurring within 30 days of permanent discontinuation of antithrombotic study medication will be the focus for the assessment of potential rebound effects.

Data collected with the International Physical Activity Questionnaire (IPAQ) and the Diet Questionnaire will be listed in the Appendix of the Clinical Study Report. Further analyses will be reported in a separate report.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

6.4.1 Primary Safety

6.4.1.1 Primary Safety Variable

The primary safety variable is the time (in days) from randomization to the first occurrence of the following primary safety outcome:

modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding, defined as:

- fatal bleeding, and/or

  symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, respiratory, liver, pancreas, adrenal gland or kidney, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring reoperation, and/or

- bleeding leading to hospitalization

The primary safety time-to-event variable will be derived in a manner similar to that described in Section 6.2.1.1 for the primary efficacy variable.

In addition to the analysis and censoring scheme according to the intention-to-treat principle, secondary safety analyses will be performed using time-to-event variables with censoring according to the censoring schemes for secondary safety analyses as described in Section 4.5.3.

6.4.1.2 Primary Safety Analysis

The principal analysis of the primary safety outcome will be based on the intention-to-treat principle. The analysis will follow similar methodology as the analysis of the primary efficacy outcome described in Section 6.2.1.2.

In addition, the primary safety outcome will be analyzed based on the safety analysis set and the secondary safety data scopes and corresponding censoring rules defined in Sections 4.5.2 and 4.5.3.

The number of subjects with multiple primary safety outcomes will be summarized, and further analyzed if applicable. Further details characterizing the bleeding events collected on the Bleeding CRF Report will be summarized by means of descriptive statistics and frequency tables.

6.4.1.3 Safety Subgroup Analyses

Subgroup analyses for the primary safety outcomes will be performed based on ITT analysis set and scope and based on the safety analysis set and treatment-emergent data scope similar to the methodology outlined in Section 6.2.5.

6.4.2 Other Safety Analyses

For the purposes of this trial, the following events will be captured on the CRF as study outcome events and will be reported as primary, secondary, or tertiary outcomes or as outcome of the pantoprazole randomization (see Section 6.2):

> cardiovascular death, myocardial infarction, stroke, major bleeding, cardiovascular hospitalization, venous thromboembolism, revascularization, amputation, angina, heart failure, resuscitated cardiac arrest, new diagnosis (/recurrence) of cancer, gastrointestinal bleeding, ulcer, perforation, or obstruction, and other expected non-cardiovascular causes of hospitalization and death.

6.4.2.1 Adverse Events

A Serious Adverse Event / Event of Special Interest (SAE/ESI) CRF Report is to be completed when a subject has an event that is (a) not an exempted study outcome and serious, or (b) an event of special interest. In addition, any AEs of particular concern to the investigator may be recorded on the CRF. While AEs that are not serious but that lead to permanent discontinuation of study medication will be captured in the CRF, non-serious AEs that do not lead to discontinuation of study medication will not be collected.

Additional hospitalization data will be collected on the CRF to permit the analysis of MRU data, which will be reported separately in another stand-alone report.

Analyses of reported adverse events will be performed based on

- the ITT analysis set using the “ITT” data scope
- the safety analysis set and the “treatment emergent outcomes” data scope[77]

as outlined in Section 4.5.2.

[77] Text modified as per modification 4 in integrated SAP, Version 4.1.

In case of uncertainty (e.g., missing or incomplete dates), adverse events will be classified as "treatment emergent" and be included in the ITT scope following the worst case approach. In addition, those AEs occurring during the run-in phase and those AEs occurring after discontinuation of anti-thrombotic study treatment will be summarized, respectively.[78]

The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest with onset at the date of or after randomization will be summarized by means of AE tables.

For each AE and serious adverse event (SAE), the number and percentage of subjects who experienced at least 1 occurrence of the given event will be tabulated according to the affected primary system organ class (SOC) and preferred term (PT) by randomized antithrombotic study treatment group. A total column will be included in all safety summaries. After study close-out for the pantoprazole/placebo portion of the study, similar tables will display the same information by PPI study treatment group, see also analyses described in Section 5.

Frequency tables, showing an overall summary of number of subjects with AEs and SAEs, will be given, and will include the following information.

- if AE (/ SAE) occurred with causal relationship to study drug separately for each study medication, i.e., rivaroxaban/rivaroxaban placebo, aspirin/aspirin placebo, and pantoprazole/pantoprazole placebo,
- maximum intensity for any AE / any study-drug related AE,
- AE related deaths,
- discontinuation of study treatment use due to AE (as well as due to SAE).

A similar table showing overall summary information of AEs during run-in will be given.

In addition, frequency tables will summarize the number of subjects with

- any event occurring within 30 days before permanent study drug discontinuation
- any event occurring more than 2 days after permanent study drug discontinuation

for antithrombotic study medication.

6.4.2.2 Death

Deaths will be summarized by cardiovascular cause and non-cardiovascular cause and sub-categories as specified in the Death CRF Report.

6.4.2.3 Pregnancies

Any pregnancy occurring in a study subject (or in partners of study subjects) during the subject's participation in this study will be displayed.

[78] Text modified as per modification 4 in integrated SAP, Version 4.1.

6.4.2.4 Vital Signs

Systolic and diastolic blood pressure (in mm Hg) for both left and right arm as well as left and right ankle and heart rate, and other physical measurements (weight, height, hip circumference, and waist circumference) obtained at screening/run-in, at the 2 Year Visit, the Final rivaroxaban/aspirin Follow-up Visit and at the Final Follow-up Visit will be displayed by means of descriptive statistics.

6.4.2.5 Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be provided for each laboratory parameter as follows:

- Serum creatinine and estimated glomerular filtration rate (eGFR) at Screening/Run-in Visit
- Serum creatinine and eGFR at randomization (planned 4-7 days after CABG)
- Total cholesterol at Screening/Run-in Visit
- Cardiac markers for MI events
- Brain natriuretic peptide (BNP)and NT-proBNP for heart failure events, if available

Results from laboratory samples for the COMPASS-MIND substudy will be summarized separately for the subgroup of subjects participating in the substudy by antithrombotic study treatment.

7. Sample Size Considerations - Amended[79]

In this trial, it was originally planned to randomize at least 19,500 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome with the objective to achieve at least 90% power to detect a 20% RRR for each of the 2 rivaroxaban-based treatment groups vs. the common aspirin-control group. The total number of events needed under the original assumptions made in the protocol, version 1.1, dated 28 November 2012, is shown in Table 7-1 for different scenarios depending on the assumed annual incidence rate in the aspirin group. Due to the event-driven study design, the number of randomized subjects, length of enrollment and total study duration may vary. It was specified in the protocol that a larger number of subjects may be recruited, if recruitment is going well. All numbers below (in Table 7-1 and the conclusion) refer to the minimum number of events to be observed after successful completion of the run-in period. For the total number of subjects to be enrolled in the run-in period, at least 10% must be added to the total number below.

Original assumptions for antithrombotic treatment randomization were:

- 3-group study with 1:1:1 randomization
- In total, a minimum of 19,500 subjects will be randomized (at least 6,500 subjects per treatment group) according to a 1:2:3:4:4 pattern within 2.5 years
- 2-sided type I error level of 2.7% for each of the two comparisons to control the overall type I error level of 5%

[79] Text in this section revised based on changes in the integrated CSPs, Versions 2.0 and 3.0.

- Constant annual incidence rate in aspirin-control group between 4.0% and 4.5%
- Effect size: 20% relative risk reduction to be detected for each comparison
- Intention-to-treat analysis: all subjects randomized are included in the analysis as randomized and the follow-up period for each subject is as long as possible from randomization until the date of the Final Follow-up Visit for each subject
- Length of recruitment period is about 2.5 years
- Early discontinuation of study drug: about 6% and 4% in the 1st and 2nd 6-month periods, respectively, and 3% in the 6-month periods thereafter

The expected total number of observed events and the estimated power for each of the two comparisons are displayed in Table 7-1.

Table 7-1. Events calculations – CSP Version 1.1

Assumed annual incidence rate in aspirin-control group	Expected total study duration (years)	Estimated power for one comparison	Expected total number of events
4.0%	4.5 5.0	90.6% 93.6%	1,923 2,227
4.5%	4.5 5.0	93.6% 95.9%	2,150 2,488

Based on these estimates and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban treatment groups, with at least 90% power, it was planned to randomize at least 19,500 subjects and to continue the study until a minimum of 2,200 subjects experience an unrefuted[80] event for the primary efficacy outcome. In this multi-center study, each center is expected to randomize at least 50 subjects.

As explained in the integrated CSP, Version 2.0, the sample size was increased by protocol Amendment 6. Based on emerging data from the ORIGIN trial and the TRA2P-TIMI 50 (vorapaxar) secondary prevention trial, a realistic incidence rate was found to be 3.5-4.0% rather than 4.0-4.5%. Keeping all other assumptions as in the original CSP, Version 1.1, but assuming

- that, in total, a minimum of 21,400 subjects are randomized (approximately 7,134 subjects per treatment group) and
- a constant annual incidence rate in the aspirin control group between 3.0% and 4.0%,

the expected total number of observed events and the estimated power for each of the two comparisons are displayed in Table 7-2.

[80] Text modified as per modification 1 in integrated SAP, Version 3.0.

Table 7-2. Events calculations – Integrated CSP, Version 2.0

Assumed annual incidence rate in aspirin control group	Expected total study duration (years)	Estimated power for one comparison	Expected total number of events
3.0%	4.5	85.1%	1,642
	5.0	89.2%	1,909
3.5%	4.5	90.2%	1,907
	5.0	93.4%	2,215
4.0%	4.5	93.7%	2,171
	5.0	96.0%	2,517

Based on these estimates, it was then planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an unrefuted[81] event for the primary efficacy outcome.

However, during the first 2 years after randomization of the first patient, it was found that the actual randomization was slower than expected and that the observed cumulated overall annual incidence was at the lower end of the projected range of 3.0 to 4.0%. This led to the decision to continue enrollment and to thereby roughly maintain the study duration in the originally planned range of 4.5 to 5 years. Simulations were performed to justify the implied sample size increase, based on the following revised assumptions, which are partially taken from the blinded data observed within the first 2 years of the trial:

- In total, a minimum of 27,400 subjects are randomized (approximately 9,134 subjects per treatment group)
- Overall length of recruitment period about 3 to 3.5 years, where randomization times are
  - taken as observed for the first ~18,000 subjects
  - assumed to be approximately uniform over about 10 months with some seasonal variation for the remaining ~9,400 subjects
- 2-sided overall type I error level of 5% using a truncated Hochberg test ($\gamma = 0.9$) for the testing of the two primary hypotheses
- Constant overall incidence rate of about 2.9% per year (95% CI: 2.56 – 3.22%), resulting in a constant incidence rate of about 3.3% (95% CI: 2.95 – 3.71%) per year for the aspirin control group assuming a 20% relative risk reduction for both hypotheses
- Early discontinuation of study drug: about 6% and 4.5% in the 1st and 2nd 6-month periods, and 3% in the 6-month periods thereafter
- Censoring due to non-CV death at an event rate of almost 1% per year
- The study is continued until a minimum of 2,200 subjects experience an event for the primary efficacy outcome

The simulation results under these assumptions, based on 3,000 repetitions, are displayed in Table 7-3.

[81] Text added as per modification 1 in integrated SAP, Version 3.0.

Table 7-3. Estimated power and time to 2,200 subjects with primary outcome

Assumed annual incidence rate in aspirin control group	Projected time from first patient randomized to 2,200 subjects experienced primary outcome event	Estimated power for at least one significant primary comparison	Estimated power for both comparisons significant
2.95%	5 years, 7-8 months	98.17%	92.13%
3.32%	4 years, 9-10 months	98.27%	92.97%
3.71%	4 years, 6 months	98.40%	93.63%

Based on these simulation results, the sample size was increased by CSP Amendment 8. It is planned to randomize at least 27,400 subjects and to continue the study until a minimum of 2,200 subjects experience an unrefuted[82] event for the primary efficacy outcome.

Assumptions for pantoprazole randomization are:

- Annual incidence rate for major upper gastrointestinal complications (overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction or perforation) in the range of 1.6% to 2.2%
- At least 16,440 (as per integrated CSP, Version 2.0) subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in a 1:1 ratio
- 2-sided type I error level of 5%
- Effect size: 50% relative risk reduction to be detected
- Intention-to-treat analysis: all subjects randomized are included in the analysis as randomized and the follow-up period for each subject is as long as possible from randomization until the date of the individual subject's Final Follow-up Visit

Under these assumptions, the expected total number of major upper gastrointestinal complications is between 570 and 780, depending on the observed incidence rates and the total study duration. The estimated power for the detection of the true relative risk reduction of about 50% for major upper gastrointestinal complications for pantoprazole 40 mg od vs. pantoprazole placebo is close to 100% for all scenarios considered.

Sample size estimation was based on the method by Lakatos (Lakatos, 1988 [11]) implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis Software (SAS) macro provided by Shih (1995) (20). In addition, simulations were performed to (1) confirm that the Dunnett step-up testing procedure (Dunnett and Tamhane, 1992 [2]) as originally planned for the analysis of the primary efficacy outcome as well as (2) the mixture gatekeeping procedure as described in Section 6.2 for the analysis of the primary efficacy outcome keeps the overall type I error level of 5%. SAS calculations and simulations were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, NC, USA).

[82] Text added as per modification 1 in integrated SAP, Version 3.0.

8. Document History and Changes in the Planned Statistical Analysis

- SAP, version 1.0, dated January 10, 2013 (without attachments) approved on January 10, 2013:
    - approved core SAP document for submission to US FDA.

8.1 Overview Changes to SAP – Amendment 1

The SAP, Version 1.0, dated 10 January 2013, was amended with the changes resulting from global CSP amendments. An integrated statistical analysis plan was prepared.

- Integrated statistical analysis plan, version 2.0, dated August 19, 2015 (without attachments):
    - This document was revised to reflect the CSP modifications, additions, and deletions resulting from
      - global amendment 6, forming integrated CSP Version 2.0, dated 03 July 2014, and
      - global amendment 8, forming integrated CSP Version 3.0, dated 19 August 2015.
    - SAP modifications resulting from the integrated CSP Version 2.0 are primarily
      - administrative, editorial, typographical, and consistency-related corrections,
      - minor clarifications for the secondary and tertiary efficacy outcomes,
      - sample size increase based on emerging data external to the COMPASS trial,
      - addition of CABG specific objectives,
      - clarifications in the discontinuations of subjects from study treatment, and
      - timing and tabulated overview.

      The SAP, version 1.0, was not immediately amended after approval of the integrated CSP, version 2.0, since an FDA Advice Letter, dated 29 August 2014, had triggered further discussions affecting statistical topics.
    - SAP modifications resulting from the integrated CSP Version 3.0 are primarily
      - a change in secondary and tertiary efficacy outcomes,
      - a change in testing strategy to control familywise type I error rate for testing of primary and secondary hypotheses,
      - sample size increase to maintain study timelines as originally planned given lower incidence in the primary efficacy outcome and slower randomization than originally expected, and
      - a revision of the description of the interim analysis.

8.2 Overview Changes to SAP – Amendment 2

Editorial, administrative, and typographical corrections were made that do not affect the overall integrated SAP. These changes are not described in this section.

The following changes are introduced in SAP Version 3.0.

Modification 1: Introduction of the terminology “unrefuted event”.

Rationale: CSP and SAP were not yet referring to the harmonized terminology resulting from the event adjudication plan, version 3.0. According to the event adjudication plan, a reported and adjudicated event is designated “unrefuted” if it does meet the specified definition or “refuted” if it does not. The wording “verified” event from the original SAP has been revised to reflect the harmonized terminology.

Sections affected:

- Section 3: Study Design
- Section 4.1: General Principles
- Section 4.4: Interim Analyses and Data Monitoring
- Section 4.5.1: Analysis Dates
- Section 4.5.3: Censoring Rules for Time-to-Event Variables
- Section 6.2.1.1: Primary Efficacy Variable
- Section 7: Sample Size Considerations – Amended

Modification 2: Clarification of data scope.

Rationale: Clarification that all data collected for a randomized subject until end of study, or until the time of loss to follow-up, or complete refusal to provide additional information will be used for the statistical analysis.

Sections affected:

- Section 4.5.2: Data Scopes

Modification 3: Time window for second look in interim analysis.

Rationale: The time window for the second look after crossing the monitoring boundary in the interim analysis was not consistent with the DSMB Charter, which states 3 months. Therefore, the time window in the SAP was made a little more flexible to allow for 3-6 months instead of 4-6 months.

Sections affected:

- Section4.4: Interim Analyses and Data Monitoring

Modification 4: ITT analysis set and unique randomized subjects.

Rationale: After completion of the randomization phase for the study, it has been detected that few subjects have unintentionally been randomized twice in the study, some at a different site from the first. Therefore, the definition of the ITT analysis set was amended by adding that only unique subjects will be considered. In the analysis, these subjects will be considered with the treatment to which they have randomly been assigned at the initial site. Data from the randomization at the second site will be documented and reported.

Sections affected:

- Section 5.1.1: Intention-to-Treat Analysis Set (ITT)

Modification 5: Subgroup variables.

Rationale: Additional subgroups and clarifications for existing subgroups variables have been added. Furthermore, important subgroups have been distinguished from other subgroups that are examined to assess the consistency of a treatment effect.

Sections affected:

- Section 6.1.6: Other Baseline Characteristics
- Section 6.2.5: Efficacy Subgroup Analysis

Modification 6: Pantoprazole outcomes.

Rationale: Observational studies have associated pantoprazole use with a range of adverse outcomes. Therefore, it is now of interest to explore the effect of pantoprazole compared with placebo on these outcomes in the COMPASS study.

Sections affected:

- Section 6.2.4.1: Variables for Pantoprazole Randomization

Modification 7: Analysis of the joint effect and/or interaction of study treatments.

Rationale: A subheader for the section describing the additional analysis of the joint effect and/or interaction between rivaroxaban-based anti-thrombotic therapy and proton pump inhibitor use on the primary efficacy outcome was added to better structure the section and emphasize this type of analysis.

Sections affected:

- Section 6.2.1.2: Primary Efficacy Analysis

Modification 8: MI type criteria according to universal definition of myocardial infarction.

Rationale: As far as possible based on the collected data, type of MI will also be determined based on the MI type criteria according to the universal definition of myocardial infarction. Details will described in the derivation document. The efficacy outcomes will then be evaluated by MI types according to the universal definition.

Sections affected:

- Section 6.2.7: Exploratory Analysis

8.3 Changes to SAP Text by Amendment 2

- Changes as a result of Modification 1 in Sections 3, 4.4, 4.5.1, 4.5.3, 6.2.1.1, and 7.

  Old Text (1):

  […] ~~a verified~~ event […]

  New Text (1):

  […] an outcome event […]

Old Text (2):

[…] ~~a verified~~ event […]

New Text (2):

[…] an unrefuted event […]

Old Text (3):

[…] an event […]

New Text (3):

[…] an unrefuted event […]

- Changes as a result of Modification 1 in Section 4.1.

  Added Text:

  Primary outcome events (myocardial infarction, stroke, CV death), selected secondary and tertiary outcome events (acute limb ischemia, heart failure, venous thromboembolism, cancer), as well as bleeding and GI events will undergo an event adjudication process to evaluate whether events reported by investigators meet the pre-specified trial definitions. A reported and adjudicated event is designated "unrefuted" if it does meet the specified definition or "refuted" if it does not. Primary statistical analyses will be based on unrefuted events. In addition, all reported events will summarized.

- Changes as a result of Modification 2 in Section 4.5.2.

  Added Text:

  The analysis will be based on all data collected for a randomized subject until end of study, or until the time of loss to follow-up, or complete refusal to provide additional information.

- Changes as a result of Modification 3 in Section 4.4.

  Old Text:

  If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be done after at least an additional 4-6 months to confirm the boundary remains crossed and that the trend in treatment effect is not temporary.

  New Text:

  If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be done after at least an additional 3-6 months to confirm the boundary remains crossed and that the trend in treatment effect is not temporary.

- Changes as a result of Modification 4 in Section 5.1.1.

  New Text:

  The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all unique randomized subjects.

If a subject is unintentionally randomized twice in the study, the subject will be included in the statistical analysis with the ID from the site where the initial randomization took place. Data from the randomization at the second site will be documented and reported.

- Changes as a result of Modification 5 in Section 6.1.6.

  Old Text:

  The number of subjects falling in the categories of the ~~following~~ list of ~~(~~subgroup~~)~~ variables will be summarized by means of frequency tables, by both randomized antithrombotic and pantoprazole study treatment groups and overall.

  - ~~Coronary artery disease (yes, no)~~
  - ~~Peripheral artery disease (yes, no)~~
  - ~~CAD and PAD (yes, no)~~
  - ~~CAD only, PAD only, CAD and PAD~~
  - ~~CABG surgery (planned within 4-7 days) before randomization (yes, no)~~
  - ~~Region (North America, Western Europe, Eastern Europe, Asia Pacific and other, and South America; see Appendix 10.1)~~
  - ~~History of a prior heart failure (yes, no)~~
  - ~~History of non-lacunar ischemic stroke ≥1 months ago (yes, no)~~
  - ~~Age (<55, 55 - <65, 65 - 75, >75 years)~~
  - ~~Baseline renal function (estimated glomerular filtration rate <60, ≥60 mL/min)~~
  - ~~Baseline diabetes (yes, no)~~
  - ~~Smoking status at baseline (smoker, nonsmoker)~~
  - ~~Baseline proton pump inhibitor use (yes, no)~~
  - ~~Peptic ulcer history at baseline (yes, no)~~

  New Text:

  The number of subjects falling in the categories of the list of subgroup variables, see subsection 6.2.5, will be summarized by means of frequency tables, by both randomized antithrombotic and pantoprazole study treatment groups and overall.

- Changes as a result of Modification 5 in Section 6.2.5.

  Old Text:

  Homogeneity of treatment effect (i.e., the effect of antithrombotic study treatment on the primary efficacy outcome and effect of pantoprazole study treatment on the pantoprazole outcome) will be examined for the following subgroup variables:

  - Coronary artery disease (yes, no)
  - Peripheral artery disease (yes, no)
  - CAD and PAD (yes, no)
  - CAD only, PAD only, CAD and PAD

- ~~CABG surgery (planned within 4-7 days) before randomization (yes, no)~~
- ~~Any prior CABG (yes, no), further subdivided as CABG days 4-7 before randomization and other prior CABG~~
- Region ~~(~~North America, Western Europe, Eastern Europe, Asia Pacific and other, and South America~~)~~
- History of a prior heart failure (yes, no)
- History of non-lacunar ischemic stroke ~~≥1 months ago~~ (yes, no)
- Sex (male, female)
- Age ~~(~~<55, 55 - <65, 65 - 75, >75 years~~)~~
- Race (White or Caucasian, Black or African American, Asian, other)
- Baseline renal function (estimated glomerular filtration rate <60, ≥60 mL/min)
- Baseline diabetes (yes, no)
- Smoking status at baseline (~~smoker, nonsmoker~~)
- Baseline proton pump inhibitor use (yes, no)
- Peptic ulcer history at baseline (yes, no)

Additional subgroup analyses, if identified, will be specified before unblinding of treatment assignment. […].

No interactions with any of the subgroup variables are expected. If the interaction term is significant at the 5% type I error level in the analysis of the primary efficacy outcome, secondary and tertiary efficacy outcomes will be investigated to evaluate the plausibility of such an effect. […]

New Text:

Homogeneity of treatment effect (i.e., the effect of antithrombotic study treatment on the primary efficacy outcome and effect of pantoprazole study treatment on the pantoprazole outcome) will be examined for the following subgroup variables, where important subgroups are distinguished from "other" subgroups that are examined to assess the consistency of a treatment effect:

Important subgroups

- Coronary artery disease (yes, no)
- Peripheral artery disease (yes, no)
- CAD and PAD (yes, no)
- CAD only, PAD only, CAD and PAD
- History of prior asymptomatic carotid artery stenosis >= 50%/revascularization (yes, no)
- History of polyvascular disease with number of vascular beds affected [CAD, PAD, cerebrovascular disease, i.e., prior stroke or asymptomatic carotid artery stenosis >= 50%/revascularization] (1, 2, or 3 vascular beds affected)
- Prior CABG surgery

  - Any prior CABG surgery (yes, no)
  - Study baseline CABG surgery [planned within 4-7 days before randomization] (yes, no)
  - Prior CABG surgery (no prior CABG surgery, study baseline CABG surgery, other history of prior CABG surgery)
- CAPRIE-like population with medical history of any of the following prior events: MI, (ischemic) stroke, or PAD (yes, no)
- History of prior MI (yes, no)
- History of both prior MI and polyvascular disease or multivessel CAD (yes, no)

Other subgroups

- Region
  - North America, Western Europe, Eastern Europe, Asia Pacific and other, and South America, see Appendix 10.1
  - US, non-US
- Sex (male, female)
- Age
  - Categories 1: <55, 55 to <65, 65 to 75, >75 years
  - Categories 2: < 65, ≥ 65 to < 75, ≥ 75 years
- Race (White or Caucasian, Black or African American, Asian, other)
- Body weight at baseline (≤ 60 kg, > 60 kg)
- Baseline renal function
  - estimated glomerular filtration rate (eGFR) categories 1: <60, ≥60 mL/min
  - eGFR categories 2: < 15, 15 to < 30, 30 to < 60, ≥ 60 mL/min
  - eGFR categories 3: < 30, 30 to 50, >50 to 80 ml/min, >80 ml/min
- Smoking status
  - Tobacco use at baseline (yes, no)
  - History of tobacco use (yes, no)
- Baseline proton pump inhibitor use (yes, no)
- Baseline lipid lowering agent use (yes, no)
- Baseline diabetes (yes, no)
- History of a prior heart failure (yes, no)
- History of peptic ulcer (yes, no)
- History of (non-lacunar ischemic) stroke (yes, no)
- History of peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty (yes, no)
- History of limb or foot amputation for arterial vascular disease (yes, no)
- History of hypertension (yes, no)

- History of prior coronary PTCA/Atherectomy/PCI (yes, no)
- History of prior MI and age < 65 years (yes, no)
- History of prior MI and reduced renal function, i.e., eGFR <60 mL/min (yes, no)

Additional subgroup analyses, if identified, will be specified before unblinding of treatment assignment. […].

No interactions with any of the subgroup variables are expected. If,

- for important subgroups: the interaction term is significant at the 5% type I error level in the analysis of the primary efficacy outcome,
- for other subgroups: the interaction term is significant at the 1% type I error level in the analysis of the primary efficacy outcome and there is a biologically coherent explanation for the finding,

  secondary and tertiary efficacy outcomes will be investigated to evaluate the plausibility of such an effect. […]

- Changes as a result of Modification 6 in Section 6.2.4.1.

  Old Text:

  Variable for Pantoprazole Randomization

  The variable for the pantoprazole randomization is the time (in days) from randomization to the first occurrence of the following outcomes:

  - Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
  - Overt upper gastrointestinal bleeding of unknown origin
  - Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL
  - Symptomatic gastroduodenal ulcer
  - Gastrointestinal pain with underlying multiple gastroduodenal erosions, obstruction or perforation

  The time-to-event variable will be derived in a similar manner as described in Section 6.2.1.1 for the primary efficacy variable.

  New Text:

  Variables for Pantoprazole Randomization – Amended

  The main variable for the pantoprazole randomization is the time (in days) from randomization to the first occurrence of the following outcomes:

  - Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
  - Overt upper gastrointestinal bleeding of unknown origin
  - Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL
  - Symptomatic gastroduodenal ulcer

- Gastrointestinal pain with underlying multiple gastroduodenal erosions, obstruction or perforation

The time-to-event variable will be derived in a similar manner as described in Section 6.2.1.1 for the primary efficacy variable.

Other outcomes of interest for the pantoprazole randomization are:

- pneumonia, enteric infections, and bone fractures as well as new diagnosis of gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, and dementia since randomization.

- Changes as a result of Modification 7 in Section 6.2.1.2.

  Added Text:

  Analysis of the joint effect and/or interaction of study treatments

- Changes as a result of Modification 8 in Section 6.2.7.

  Added Text:

  The efficacy outcomes will also be evaluated by MI types according to the universal definition, see derivation document for details.

8.4 Overview Changes to SAP – Amendment 3.0

The SAP Version 4.0 (including SAP amendment v3.0) was written after the first interim analysis with the intent to fully preserve the statistical analyses that have been outlined in the protocol and the previous version of the SAP but to clarify some aspects pertaining to the interim analysis and to reflect the wording and additional close-out visits prompted by the premature stop of the anti-thrombotic study treatment arms.

Version 4.0 of the SAP was contentwise finalized on 17 March 2017. During the approval process, an open question was raised and the approval process was put on hold on 21 March 2017. As not all approvers, including the principal investigator, had signed off Version 4.0, this version is not considered to be in effect or approved. The withdrawn document is retained without changes together with a memo and the available signature forms. A revised version 4.1 of the integrated SAP was prepared instead.

8.5 Overview Changes to SAP – Amendment 3.1

Editorial, administrative, and typographical corrections were made that do not affect the overall integrated SAP. These changes are not described in this section.

The following changes are introduced in SAP, Version 4.1.

Modification 1: Early close-out of the rivaroxaban/aspirin portion of the trial.

Rationale: Some aspects pertained to the interim analysis, wording, and design amendments prompted by the premature stop of the anti-thrombotic study treatment arms are clarified. These changes include the description of additional study visits, dates, data scopes and rules due to the early close-out of the rivaroxaban/aspirin portion of the trial. In addition, it is described that the

analyses pertained to the pantoprazole/placebo randomization will be deferred to a later date at the end of the study.

Sections affected:

- Section 3: Study Design
- Section 4.2: Handling of Non-Compliance to Study Treatment or Follow-up
- Section 4.5: Data Rules
- Section 5.1.2: Safety Analysis Set
- Section 6.1.1: Disposition
- Section 6.1.7: Prior and Concomitant Medication
- Section 6.1.8: Extent of Study Follow-up and Exposure
- Section 6.2.1.1: Primary Efficacy Variable
- Section 6.2.1.2: Primary Efficacy Analysis
- Section 6.2.3.2: Tertiary Efficacy Analysis
- Section 0: Analysis for Pantoprazole Randomization
- Section 6.2.4.1: Variables for Pantoprazole Randomization
- Section 6.2.5: Efficacy Subgroup Analysis
- Section 6.2.6: Analyses of the COMPASS MIND Substudy

Modification 2: Type I error at first interim analysis.

Rationale: Details regarding the type I error at the first interim analysis or testing of secondary hypotheses after premature stopping for efficacy according to the modified Haybittle-Peto boundary had not been specified in the SAP. A clarification of the type I error at the first interim analysis has been added.

Sections affected:

- Section 6.2: Efficacy

Modification 3: SAS code – stratified log-rank test.

Rationale: The SAS code provided for carrying out the stratified log-rank test has been updated to reflect the FDA preferred implementation, with the difference being how tied event times are handled.

Sections affected:

- Section 6.2.1.2: Primary Efficacy Analysis

Modification 4: Clarification of data scopes and timing of AE data summaries.

Rationale: Safety analyses for variables related to bleedings will be performed on all safety data scopes defined. The data scopes for summaries of AE data have been adapted to the study design and the two portions of the study after the interim analyses.

Sections affected:

- Section 6.4.2.1: Adverse Events

Modification 5: Sensitivity analyses to address potential impact of missing data on primary analysis.

Rationale: As already described in Section 6.2.7 of the SAP, Version 1.0, it was planned to perform additional sensitivity analyses in order to evaluate the robustness of the primary analysis. A detailed description of the planned sensitivity analyses has been added in Appendix 10.4.

Sections affected:

- Section 6.2.7: Exploratory Analyses
- Section 10.4: Sensitivity analyses to address the potential impact of missing data

Modification 6: Regions.

Rationale: The allocation of countries to regions has been revised.

Sections affected:

- Section 10.1: Regions

Modification 7: Net clinical benefit.

Rationale: A net clinical benefit variable has been added to the SAP.

Sections affected:

- Section 6.2.2.1: Secondary Efficacy Variables

8.6 Changes to SAP Text by Amendment 3

- Changes as a result of Modification 1 in Section 3:

  Old Text:

  […]

  Final Follow-up Visit and end of study

  The ~~primary~~ analysis will be based on the events that occur after the date and time of randomization and up until the Final Follow-up Visit. ~~The date of the Final Follow-up Visit cannot be pre-determined as this study is event-driven, but the visits will be scheduled when at least 2,200 subjects have experienced an unrefuted event (after adjudication) for the primary efficacy outcome for the rivaroxaban randomization. These events are expected to accumulate over approximately 4-5 study years after randomization of the first subject. All subjects~~ will remain in follow-up until ~~this minimum number of primary outcome events has been reached~~, irrespective of whether they are still taking study treatments or whether they have experienced an outcome. […]

End of Washout Visit

A ~~final~~ Washout Visit (End of Washout Telephone Visit) […]

New Text:

Final rivaroxaban/aspirin Follow-up Visit

The primary analysis will be based on the events that occur after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (February 06, 2017, the date of the DSMB recommendation to stop the rivaroxaban/aspirin study treatment arms). At the Final rivaroxaban/aspirin Follow-up Visit, subjects will be asked to stop taking all randomized rivaroxaban and aspirin study treatment, while study treatment with randomized pantoprazole/pantoprazole placebo can continue as planned.

Rivaroxaban/aspirin Washout Telephone Visit

A rivaroxaban/aspirin Washout Telephone Visit will be conducted by telephone about 30 days after the Final rivaroxaban/aspirin Follow-up Visit to collect information on outcomes and protocol specific adverse events.

Note: the rivaroxaban/aspirin Washout Telephone Visit is equivalent to the end of study for those subjects who have not been randomized to pantoprazole/placebo.

Final (pantoprazole/placebo) Follow-up Visit and end of study

The analysis, as pertains to the pantoprazole randomization, will be based on the events that occur after the date and time of randomization and up until the Final Follow-up Visit, also referred to as "Final pantoprazole/placebo Follow-up Visit". Subjects ongoing in the pantoprazole arms will remain in follow-up until the end of study, irrespective of whether they are still taking study treatments or whether they have experienced an outcome. At the Final Follow-up Visit the following information will be obtained from the subject: study treatment adherence, study treatment interruption, outcomes and adverse events, physical measurements and concomitant medications, and questionnaires (except for the Interheart Diet Questionnaire and the IPAQ). Subjects will be asked to stop taking randomized pantoprazole study treatment. The Final Follow-up Visit (close out is expected to occur over a period of about 3 months) and the subsequent 30-day washout period will occur nearly simultaneously (as scheduling permits) for all study subjects.

End of pantoprazole/placebo Washout Telephone Visit

A pantoprazole/placebo Washout Visit (End of Washout Telephone Visit) will be conducted by telephone about 30 days after the Final pantoprazole/placebo Follow-up Visit to collect information on outcomes and protocol specific adverse events. Adverse events will continue to be collected up to 30 days post study drug treatment with pantoprazole/placebo.

An overview describing these visits and the data to be included in different type of analyses is given in Figure 3-1.

Newly added: Figure 3-1: Study visits and analyses

Editorial changes in Table 3-2. Schedule of evaluations

- Changes as a result of Modification 1 in Section 4.2:

  Old Text:

  A randomized subject who permanently stops taking study treatment before their Final Follow-up Visit for any reason is defined as having had a premature permanent discontinuation of study treatment (including subjects who were randomized but never started taking any study treatment). The reason for permanent discontinuation of study treatments will be recorded in the CRF.

  However, all subjects will be encouraged to remain study treatments and under observation ~~the full duration of the study~~.

  New Text:

  A randomized subject who permanently stops taking study treatment before their Final rivaroxaban/aspirin Follow-up Visit (for rivaroxaban/aspirin) or their Final pantoprazole/placebo Follow-up Visit (for pantoprazole/placebo) for any reason is defined as having had a premature permanent discontinuation of study treatment (including subjects who were randomized but never started taking any study treatment). The reason for permanent discontinuation of study treatments will be recorded in the CRF. Subjects who continued on rivaroxaban/aspirin study treatment until the global rivaroxaban/aspirin outcomes cut-off date but stopped rivaroxaban/aspirin study treatment before their Final rivaroxaban/aspirin Follow-up Visit will still be considered as study rivaroxaban/aspirin follow-up completers.

  However, all subjects will be encouraged to remain on their randomized and pertinent (to the portion of the study) study treatments and under observation until the end of the study. […]

  If it is documented in the database that the subject is alive at the global rivaroxaban/aspirin outcomes cut-off date / at the end of the study, the subject will not be classified as lost to follow-up, but as alive.

- Changes as a result of Modification 1 in Section 4.5:

  Old Text:

  4.5.1 Analysis Dates

  A common trial close-out window and a close out (cut-off) date will be chosen by a study committee for the COMPASS trial. ~~They will be announced and all sites will be notified before unblinding. The announcement of the common trial close out window will be timed to ensure at least 2,200 subjects will have experienced an unrefuted event for the primary efficacy outcome for the rivaroxaban randomization within this trial.~~ All subjects will return to the clinic for a Final Follow-Up Visit within this pre-specified acceptable close-out time-window (about 3 months; period ends with the common trial close-out date, see below). […]

  - Common trial close-out date:
    The common trial close out (cut-off) date is the end date of the common trial close-out window. It is the last calendar date acceptable for counting events ~~within the primary analysis~~, prior to the washout period.
    If a subject who is unable to attend his/her Final Follow-up Visit within the acceptable common trial close-out time-window, has a trial-related contact after the common trial

close-out date, the observation period up until the common trial close-out date (inclusive) will be considered in the ~~primary~~ analysis. ~~, i.e., events that occur up until the common trial close-out date (inclusive) will be counted in the primary analysis, otherwise the subject will be censored at the common trial close-out date~~.

For each subject, the following individual analysis dates will be derived: […]

- Final Follow-Up Visit date:
  The date of the Final Follow-Up Visit for the individual subject.
  Beginning with the announcement of trial close-out, all subjects are to return to the clinic for their Final Follow-Up Visit within the pre-specified common trial close-out window (see Section 3 for the schedule of evaluations at the Follow-Up Visit). If subjects do not have a Final Follow-Up Visit, the date will be missing. ~~For subjects who have a Final Follow-up Visit, events that occur after the date and time of randomization and up until the Final Follow-up Visit (inclusive) will be considered in the primary analysis.~~ […]
- Date of last double-blind dose of antithrombotic study treatment:
  […] If missing or incomplete, the date of last double-blind dose of antithrombotic study treatment is set to the latest logically possible date of antithrombotic study medication administration on or before the earliest of the subject's following dates, the date of, the date of death, or the ~~common trial close-out date~~, and no earlier than the randomization date.

4.5.2 Data Scopes

[…] Data scope according to intention-to-treat principle

Analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see Section 5.1.1) and will include all outcome events that occur after the date and time of randomization and up until the Final Follow-up Visit (inclusive) for each subject. For subjects who are unable to attend the Final Follow-up Visit within the acceptable common close-out time-window (range of dates from announcement of trial close-out up to the common trial close-out date), events occurring after the common trial close-out date will not be counted ~~for primary analysis~~ (see also Section 4.5.1). Subjects will be kept in the study group to which they were randomized and the follow-up period for each subject will be as long and complete as possible. ~~This ITT data scope will be applied to the primary analysis of the primary efficacy and safety variables, following the intention-to-treat principle.~~

Additional data scopes for secondary safety analyses

[…]

- All outcome events for each subject occurring after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) ~~Final Follow-up Visit, or the common trial close-out date if subjects are unable to attend the Final Follow-Up Visit within the acceptable common close-out time-window, documented in the database~~ ("ITT" data scope) […]

New Text:

4.5.1 Analysis Dates

A common trial close-out window and a close out (cut-off) date will be chosen by a study committee for the COMPASS trial. All subjects will return to the clinic for a Final Follow-Up Visit within this pre-specified acceptable close-out time-window (about 3 months; period ends with the common trial close-out date, see below).

Based on the DSMB recommendation after the first interim analysis and the early close-out of the rivaroxaban/aspirin study treatment portion of the study, some of the previously defined analysis dates became less important or dispensable for the rivaroxaban/aspirin randomization, while additional dates had to be added.

- Rivaroxaban/aspirin arms close-out window:
  The pre-specified target calendar date range within which subjects are to return to the clinic for a Final rivaroxaban/aspirin Follow-up Visit planned to range from end of February 2017 to 15 May 2017.
- Global rivaroxaban/aspirin outcomes cut-off date:
  The global rivaroxaban/aspirin outcomes cut-off date is 06 February 2017, i.e., the date when the DSMB recommended to stop the study treatment arms rivaroxaban 2.5 mg bid + aspirin 100 mg daily, rivaroxaban 5.0 mg bid, and aspirin 100 mg daily as soon as an orderly close-out of this portion of the study could be carried out. Outcome events that occur up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) will be counted in the primary analysis, otherwise the subject will be censored at the global rivaroxaban/aspirin outcomes cut-off date.
- Common trial close-out window:
  The pre-specified acceptable calendar date range within which subjects ongoing in the pantoprazole/placebo portion of the study are to return to the clinic for a Final Follow-Up Visit (e.g. about 3 months). […]

For each subject, the following individual analysis dates will be derived:

- Randomization date:
  The date of randomization to antithrombotic treatment of the subject.
- Date of the Final rivaroxaban/aspirin Follow-up Visit:
  The date of the Final rivaroxaban/aspirin Follow-up Visit for the individual subject. If subjects do not have a Final rivaroxaban/aspirin Follow-up Visit, the date will be missing.
- Final (pantoprazole/placebo) Follow-Up Visit date:
  The date of the Final (pantoprazole/placebo) Follow-Up Visit for the individual subject. Beginning with the announcement of trial close-out, all subjects ongoing in the pantoprazole/placebo portion of the study are to return to the clinic for their Final Follow-Up Visit within the pre-specified common trial close-out window (see Section 3 for the schedule of evaluations at the Follow-Up Visit). If subjects do not have a Final Follow-Up Visit, the date will be missing.

- Rivaroxaban/aspirin Washout Telephone Visit date:
  The date of the rivaroxaban/aspirin Washout Telephone Visit for the individual subject. To be performed about 30 days after the Final rivaroxaban/aspirin Follow-up Visit.
- End of pantoprazole/placebo Washout Visit date:
  The date of the End of pantoprazole/placebo Washout Visit for the individual subject. To be performed about 30 days after the Final pantoprazole/placebo Follow-up Visit. If subjects do not have an End of pantoprazole/placebo Washout Visit, the date will be missing.
- Last contact date during rivaroxaban/aspirin portion of the study:
  The date of the last documented contact with the subject or a third party up until the maximum (later) of the subject's {date of the Final rivaroxaban/aspirin Follow-up Visit, end of rivaroxaban/aspirin Washout date}. For subjects who died after randomization but before their scheduled end of rivaroxaban/aspirin Washout date, the date of the last rivaroxaban/aspirin related contact is set to the death date.
- Date of the last follow-up contact:
  The date of the last known documented contact with the subject or a third party (including data on subject survival status)
  - up until the Final Follow-up Visit date (inclusive), if the subject attends his/her Final Follow-up Visit or
  - up until the common trial close-out date, if the subject does not attend his/her Final Follow-up Visit.
  For subjects who die (a) after randomization but before the beginning of the common trial close-out window or (b) during the common trial close-out window but before their Final Follow-up Visit takes place, the date of the last follow-up contact is set to the death date.
  This date is only applicable to analyses for pantoprazole/placebo comparisons at the end of the study. […]
- Date of last double-blind dose of antithrombotic study treatment:
  The later date of
  - the last dose of rivaroxaban/rivaroxaban placebo study medication and
  - the last dose of aspirin / aspirin placebo study medication.
  For a subject with premature permanent discontinuation of any study medication, the corresponding last dose date(s) will be obtained from the Permanent Discontinuation CRF Report. If study medication was continued until the Final rivaroxaban/aspirin Follow-up Visit, the date of the last dose of the corresponding study treatment will be the date of the Final rivaroxaban/aspirin Follow-up Visit.
  If missing or incomplete, the date of last double-blind dose of antithrombotic study treatment is set to the latest logically possible date of antithrombotic study medication administration on or before the earliest of the subject's following dates, the date of the last contact for the rivaroxaban/aspirin comparison, the date of death, or the end of the rivaroxaban/aspirin arms close-out window, and no earlier than the randomization date.
  […]

4.5.2 Data Scopes

The analysis, as pertains to the rivaroxaban/aspirin randomization, will be based on all data collected for a randomized subject until end of the rivaroxaban/aspirin portion of the study, or until the time of loss to follow-up with no indication that the subject returned, or complete refusal to provide additional information.

The analysis, as pertains to the pantoprazole/placebo randomization, will be based on all data collected for a randomized subject until end of study, or until the time of loss to follow-up, or complete refusal to provide additional information.

This section describes the coverage of the event data scopes used for the statistical analyses. Analysis sets are described in Section 5.

Data scope for rivaroxaban/aspirin randomization according to intention-to-treat principle

For the rivaroxaban/aspirin comparisons performed after the DSMB recommendation related to the results of the first interim analysis, analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see Section 5.1.1) and will include all outcome events that occur after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) for each subject. Events occurring after the global rivaroxaban/aspirin outcomes cut-off date will not be counted for primary analysis (see also Section 4.5.1). Subjects will be kept in the study group to which they were randomized. This ITT data scope will be applied to the analysis of the primary efficacy and safety variables, following the intention-to-treat principle. ("ITT" data scope)

Additional data scopes for the rivaroxaban/aspirin randomization

Sensitivity analyses for the primary efficacy outcomes will be based on all outcome events occurring after the date and time of randomization and up until the Final rivaroxaban/aspirin Follow-up Visit (inclusive) for each subject. ("Rivaroxaban/aspirin Follow-up" data scope)

Data scope for the pantoprazole/placebo randomization according to intention-to-treat principle

[…]

Additional data scopes for secondary safety analyses for the rivaroxaban/aspirin randomization

Additional secondary analyses of safety outcomes will be based on the safety analysis set (see Section 5.1.2). Subjects will be kept in the study group to which they were randomized. Additional data scopes will be defined to include all outcome events as follows:

- All outcome events for each subject occurring after the date and time of randomization and up until the global rivaroxaban/aspirin outcomes cut-off date (inclusive) ("ITT" data scope)
- […]
- All outcome events occurring after the date and time of randomization during the entire individual rivaroxaban/aspirin follow-up and wash-out periods documented in the database ("Rivaroxaban/aspirin Follow up + Wash out" data scope)

Data scopes for safety analyses for the pantoprazole/placebo randomization

Analyses of safety outcomes for the pantoprazole randomization will be based on the safety analysis set related to the pantoprazole randomization. Subjects will be kept in the study group to which they were randomized. The outcome events will include:

- All outcome events observed from randomization until 2 days following permanent discontinuation of the pantoprazole study drug ("treatment emergent outcomes" analysis)
- All outcome events observed from randomization during the entire follow-up and wash-out periods up until the end of the trial

Corresponding censoring rules are described in Section 4.5.3.

4.5.3 Censoring Rules for Time-to-Event Variables

For any time-to-event variable in this study, the following censoring rules will be applied:

Censoring rules for analyses related to the rivaroxaban/aspirin randomization according to the intention-to-treat principle

- For analyses according to the intention-to-treat principle which are related to the rivaroxaban/aspirin randomization and performed after the DSMB recommendation, randomized subjects without documentation of an evaluable event will be censored at
    - the minimum (earliest) of the global rivaroxaban/aspirin outcomes cut-off date and the subject's last contact date during the rivaroxaban/aspirin portion of the study.

  This censoring rule will be applied to all analyses according to the intention-to-treat principle. In the rare event that for a subject only survival status information can be retrieved at the end of the study rivaroxaban/aspirin portion of the trial but no information on other outcomes, the last study rivaroxaban/aspirin follow-up contact where survival status information was obtained will still be used to determine the censoring date for the subject and if there were no known events up to then the subject will be considered as event-free.

Censoring rules for analyses related to the pantoprazole/placebo randomization according to the intention-to-treat principle

[…]

This censoring rule will be applied to all analyses related to the pantoprazole/placebo randomization performed after common trial close-out according to the intention-to-treat principle. […].

Censoring rules for secondary safety analyses related to the rivaroxaban/aspirin randomization

- For secondary safety analyses based on the safety analysis set and the ITT data scope, all randomized subjects with at least one dose of either randomized study medication and without documentation of an outcome event within the ITT data scope will be censored as stated above for study rivaroxaban/aspirin analyses according to the ITT principle.

- […]

  Note that if a subject stops treatment at the Final rivaroxaban/aspirin Follow-up Visit and experiences an event up to 2 days thereafter, the event will be counted in this analysis but not in the primary analysis using the ITT data scope.

- […]

  Note that if a subject stops treatment at the Final rivaroxaban/aspirin Follow-up Visit and experiences an event up to 30 days thereafter, the event will be counted in this analysis but not in the primary analysis.

- For secondary safety analyses based on the safety analysis set and the "Study rivaroxaban/aspirin Follow up + Wash out" data scope, all randomized subjects with at least one dose of study medication and without documentation of an outcome event will be censored at the subject's last contact date during the rivaroxaban/aspirin portion of the study.

Censoring rules for secondary safety analyses related to the pantoprazole/placebo randomization

- For "treatment-emergent" safety analyses, all randomized subjects with at least one dose of pantoprazole/placebo study medication and without documentation of an outcome event within the "treatment-emergent" data scope will be censored at the date of last dose of pantoprazole study treatment + 2 days.
- For safety analyses based on the safety analysis set and the "Follow up + Wash out" data scope, all randomized subjects with at least one dose of pantoprazole/placebo study medication and without documentation of an outcome event will be censored at the date of last trial contact.

- Changes as a result of Modification 1 in Section 5.1.2:

  Old Text:

  The safety analysis set for secondary analyses will include all randomized subjects who received at least one dose of ~~either randomized~~ study medication.

  New Text:

  The safety analysis set for secondary analyses related to the rivaroxaban/aspirin randomization will include all unique randomized subjects who received at least one dose of rivaroxaban/aspirin study medication.

  The safety analysis set for secondary analyses related to the pantoprazole randomization will include all unique randomized subjects who received at least one dose of randomized pantoprazole/placebo medication.

- Changes as a result of Modification 1 in Sections 6.1, 6.1.1 and 6.1.8:

  New Text:

  Note that all summaries related to the pantoprazole randomization described in this section of the SAP will only be provided at the end of the pantoprazole portion of the study.

[…]

The following will be tabulated overall and/or by antithrombotic treatment group:

[…]

- Number of subjects and primary reasons for premature permanent discontinuation of study medication (for each type of randomized study medication, as applicable regarding the portion of the study)

[…]

Kaplan-Meier estimates will be used to present […]

- time to the date of last double-blind dose of pantoprazole study treatment (after completion of pantoprazole/placebo portion of the study) […]

[…]

- relevant concomitant medications recorded at the Final rivaroxaban/aspirin Follow-Up Visit and the Final Follow-Up Visit.

[…]

The total duration of study follow-up for a subject in the rivaroxaban/aspirin portion of the study and overall will be calculated as follows:

- Total duration of <rivaroxaban/aspirin, study> follow-up = Date of last <rivaroxaban/aspirin, study> follow-up contact – Randomization date + 1.

- Changes as a result of Modification 1 in Section 6.2.1.1:

  Old Text:

  All unrefuted primary efficacy outcome events within the data scope according to intention-to-treat principle (see Section 4.5.2) will be considered for the derivation of the primary efficacy variable.

  - For those subjects with documentation of an unrefuted primary efficacy outcome event occurring

    ~~(a)~~ after the date and time of randomization and up until ~~the Final Follow-up Visit, or (b) after the date and time of randomization and up until the common trial close-out date, if the subject was not available for a Final Follow-up Visit up to the common trial close-out date~~

  time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:

    - the date of the subject's first primary efficacy outcome event – the randomization date + 1.

  This will constitute an uncensored observation.

  - For those subjects without documentation of an unrefuted primary efficacy outcome event within the data scope according to intention-to-treat principle,

time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:

- the ~~subject's Final Follow-Up Visit date~~ – the randomization date +1~~,~~
  ~~if the subject was available for the Final Follow-Up Visit before the common trial close-out date~~.
- ~~the subject's date of last follow-up contact up to the common trial close-out date – the randomization date +1, if~~
  ~~(a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and~~
  ~~(b) the subject's date of last trial contact is not after the common trial close-out date.~~
- ~~the common trial close-out date – the randomization date +1, if~~
  ~~(a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and~~
  ~~(b) the subject's date of last trial contact is after the common trial close-out date.~~

New Text:

All unrefuted primary efficacy outcome events within the data scope according to intention-to-treat principle (see Section 4.5.2) will be considered for the derivation of the primary efficacy variable.

- For those subjects with documentation of an unrefuted primary efficacy outcome event occurring

  after the date and time of randomization and up until <u>the minimum (earliest) of the global rivaroxaban/aspirin outcomes cut-off date and the subject's last contact date during the rivaroxaban/aspirin portion of the study</u>

time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:

- the date of the subject's first primary efficacy outcome event – the randomization date + 1.

This will constitute an uncensored observation.

- For those subjects without documentation of an unrefuted primary efficacy outcome event within the data scope according to intention-to-treat principle,
  time (in days) from randomization to the first occurrence of the primary efficacy outcome will be derived as:
  - the <u>minimum (earliest) of {the global rivaroxaban/aspirin outcomes cut-off date, the subject's last contact date during the rivaroxaban/aspirin portion of the study}</u> – the randomization date +1.

- Changes as a result of Modification 1 in Section 6.2.1.2:

  New Text:

  <u>Sensitivity analyses</u>

Sensitivity analyses will be performed to include all primary efficacy outcome events up until the minimum (earliest) of the Final rivaroxaban/aspirin Follow-up Visit date and the subject's last contact date during the rivaroxaban/aspirin portion of the study.

In addition, the number of primary efficacy outcome events occurring after the Final rivaroxaban/aspirin Follow-up Visit until the rivaroxaban/aspirin Washout Telephone Visit, included in the clean database for the rivaroxaban/aspirin comparisons, will be summarized by rivaroxaban/aspirin study treatment group.

- Changes as a result of Modification 1 in Section 6.2.3.2:

  Old Text:

  Subject reported data from the ~~SAGE, MoCA, DSS, and~~ EQ-5D questionnaire will be summarized by means of descriptive statistics and frequency tables by antithrombotic treatment group and overall and by visit. All data will be listed in the Appendix of the Clinical Study Report. In depth analyses of questionnaire data will be displayed in a separate report.

  New Text:

  Subject reported data from the EQ-5D questionnaire will be summarized by means of descriptive statistics and frequency tables by antithrombotic treatment group and overall and by visit. All data will be listed in the Appendix of the Clinical Study Report. In depth analyses of the SAGE, MoCA, and DSS questionnaire data will be displayed in a separate report/after completion of the pantoprazole/placebo portion of the study.

- Changes as a result of Modification 1 in Section 6.2.4:

  New Text:

  All analyses related to the pantoprazole randomization described in this section of the SAP will only be performed at the end of the pantoprazole portion of the study. The CSR related to the rivaroxaban/aspirin randomization will only use the pantoprazole/placebo randomization data for stratified testing and interaction analyses of efficacy / safety outcomes in relation to the rivaroxaban/aspirin randomization.

- Changes as a result of Modification 1 in Section 6.2.4.1:

  Old Text:

  The time-to-event variable will be derived in a similar manner as described ~~in Section 6.2.1.1~~ for the primary efficacy variable.

  New Text:

  The time-to-event variable will be derived in a similar manner as originally described for the primary efficacy variable.

  - For those subjects with documentation of an unrefuted pantoprazole outcome event occurring

    (a) after the date and time of randomization and up until the Final Follow-up Visit, or
    (b) after the date and time of randomization and up until the common trial close-

out date, if the subject was not available for a Final Follow-up Visit up to the common trial close-out date

time (in days) from randomization to the first occurrence of the unrefuted pantoprazole outcome will be derived as:

- the date of the subject's first unrefuted pantoprazole outcome event – the randomization date + 1.

This will constitute an uncensored observation.

- For those subjects without documentation of an unrefuted pantoprazole outcome event within the data scope according to intention-to-treat principle,
  time (in days) from randomization to the first occurrence of a pantoprazole outcome will be derived as:
  - the subject's Final Follow-Up Visit date – the randomization date +1,
    if the subject was available for the Final Follow-Up Visit before the common trial close-out date.
  - the subject's date of last follow-up contact up to the common trial close-out date – the randomization date +1, if
    (a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and
    (b) the subject's date of last trial contact is not after the common trial close-out date.
  - the common trial close-out date – the randomization date +1, if
    (a) the subject did not attend his/her Final Follow-Up Visit before the common trial close-out date and
    (b) the subject's date of last trial contact is after the common trial close-out date.

  This will constitute a right-censored observation.

- Changes as a result of Modification 1 in Section 6.2.5:

  New Text:

  The subgroup analyses for the rivaroxaban/aspirin comparisons will be performed after the end of the study rivaroxaban/aspirin portion of the trial, while subgroup analyses for the pantoprazole comparison will be performed after the end of the pantoprazole portion of the trial.

- Changes as a result of Modification 1 in Section 6.2.5:

  New Text:

  Data related to the COMPASS MIND substudy will be reported separately.

- Changes as a result of Modification 2 in Section 6.2:

  New Text:
  The recommendation by the independent DSMB to stop the rivaroxaban/aspirin arms early due to overwhelming efficacy after the first interim analysis was guided by a modified Haybittle-Peto rule, expecting "a reduction of at least 4 standard deviations in the analysis of the primary

efficacy outcome". The 2-sided type I error level corresponding to this decision rule can be calculated via $\alpha^* = \Phi(-4) + 1 - \Phi(4) = 0.0000633$, where Φ denotes the cumulative distribution function of the standard normal distribution. Considering the two comparisons, one for each rivaroxaban-treatment arm, being made according to this rule, the type I error level applied at the first interim analysis is about $\alpha_1 = 2\alpha^* = 0.0001267$.

- Changes as a result of Modification 3 in Section 6.2.1.2:

Old Text:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.05 METHOD=KM NELSON;
  STRATA stratumn;
  TEST trtgrpn;
  TIME ttevalue * ttecnsr(0);
RUN;
```

New Text:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.05 METHOD=KM NELSON;
  STRATA stratumn / GROUP=trtgrpn TEST=(LOGRANK);
  TIME ttevalue * ttecnsr(0);
RUN;
```

- Changes as a result of Modification 4 in Sections 6.4.1.3 and 6.4.2.1:

Old Text:

Subgroup analyses for the primary safety outcomes will be performed based on ~~the same analysis sets and data scopes as in the main analyses of the study~~ similar to the methodology outlined in Section 6.2.5.

[…]

Analyses of reported adverse events will be performed based on ~~the safety analysis set and all secondary safety analysis data scopes.~~ […]

In addition, frequency tables will summarize the number of subjects with

- any event occurring within 30 days before permanent study drug discontinuation
- any event occurring more than 2 days after permanent study drug discontinuation

for ~~both~~ antithrombotic study medication ~~and pantoprazole study medication~~.

New Text:

Subgroup analyses for the primary safety outcomes will be performed based on ITT analysis set and scope and based on the safety analysis set and treatment-emergent data scope similar to the methodology outlined in Section 6.2.5.

[…]

Analyses of reported adverse events will be performed based on

- the ITT analysis set using the "ITT" data scope
- the safety analysis set and the "treatment emergent outcomes" data scope

as outlined in Section 4.5.2.

In case of uncertainty (e.g., missing or incomplete dates), adverse events will be classified as "treatment emergent" and be included in the ITT scope following the worst case approach. In addition, those AEs occurring during the run-in phase and those AEs occurring after discontinuation of anti-thrombotic study treatment will be summarized, respectively.

[…] A total column will be included in all safety summaries. After study close-out for the pantoprazole/placebo portion of the study, similar tables will display the same information by PPI study treatment group, see also analyses described in Section 5.

- Changes as a result of Modification 5 in Sections 6.2.7 and 9:

  New Text

  With SAP amendment v3.0, integrated in SAP, Version 4.0, sensitivity analyses to address the potential impact of missing data on the results of the primary analysis are described in Appendix 10.4.

  […]

  Little, R J, Wang, J, Sun, X, Tian, H, Suh, E-H, Lee, M, Sarich T, Oppenheimer, L, Plotnikov, A, Wittes, J, Cook-Bruns, N, Burton, P, Gibson, C M and Mohanty, S. The treatment of missing data in a large cardiovascular clinical outcomes study. Clinical Trials, 2016; 13(3): 344–351.

  National Research Council Panel on Handling Missing Data in Clinical Trials. The prevention and treatment of missing data in clinical trials. Washington, DC: National Academy Press, 2012.

  Zhao, Y, Herring, A H, Zhou, H, Ali, M W, Koch, G G.A Multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. J Biopharm Stat. 2014 ; 24(2): 229–253.

- Changes as a result of Modification 6 in Section 10.1:

  Old Text:

  Table 10-1. Classification of countries to regions

Region	Countries
North America	Canada, USA
Western Europe	Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Sweden, Switzerland, United Kingdom
Eastern Europe	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Ukraine
Asia Pacific ~~and other~~	China, Japan, Malaysia, Philippines, South Korea, ~~Israel, South Africa, Australia~~
South America	Argentina, Brazil, Chile, Colombia, Ecuador

New Text:

Table 10-1. Classification of countries to regions

Region	Countries
North America	Canada, USA
Western Europe (and AUS/ISR/ZAF)	Australia, Belgium, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, South Africa, Sweden, Switzerland, United Kingdom
Eastern Europe	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Ukraine
Asia Pacific	China, Japan, Malaysia, Philippines, South Korea
South America	Argentina, Brazil, Chile, Colombia, Ecuador

- Changes as a result of Modification 7 in Section 6.2.2.1:

  New Text:

  In addition, a net clinical benefit time-to-event variable will be defined which is a composite of the

  - primary efficacy outcome
  - primary safety outcome, excluding bleedings leading to hospitalization and bleedings into surgical site associated with re-operation.

9. References

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10. Appendix

10.1 Regions[83]

For subgroup analyses according to region, countries will be assigned to regions as shown in Table 10-1. below. If additional countries participate in the trial, their assignment to a region will be described in an amendment to the SAP before unblinding.

Table 10-1. Classification of countries to regions

Region	Countries
North America	Canada, USA
Western Europe (and AUS/ISR/ZAF)	Australia, Belgium, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, South Africa, Sweden, Switzerland, United Kingdom
Eastern Europe	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Ukraine
Asia Pacific	China, Japan, Malaysia, Philippines, South Korea
South America	Argentina, Brazil, Chile, Colombia, Ecuador

10.2 EQ-5D

The EuroQol – a standardized instrument for use as a measure of health outcome - http://www.euroqol.org/.

Based on large population surveys, an algorithm has been developed to combine the recordings for each of these five EQ-5D dimensions into one single health state. The algorithm for the derivation of the EQ-5D health state (ranging from +1 to –0.59) using the UK value set (weights) is given below together with a worked example.

Step 1: Take the value 1.0 (equivalent to full health '11111').

Step 2: Subtract 0.081 if the state is different from '11111'.

Step 3: Subtract for each dimension the appropriate value for Level 2 or Level 3 as given in the table below (no subtraction for Level 1).

EuroQoL Dimension	Level 2	Level 3
Mobility	0.069	0.314
Self-care	0.104	0.214
Usual activity	0.036	0.094
Pain / discomfort	0.123	0.386
Anxiety / depression	0.071	0.236

[83] Tables modified based on list of participating countries as of August 2015 and modification 6 of SAP, Version 4.0.

Step 4: Subtract 0.269 if any dimension has a record of Level 3.

Example: The EQ-5D index score value for the state '11223' is given by

Step 1	*Step 2*	*Step 3*	*Step 4*		*EQ-5D index score*
1.0	minus 0.081	minus 0.036 minus 0.123 minus 0.236	minus 0.269	→	0.255

10.3 Regular and Truncated Hochberg Tests

Consider a general problem of testing m null hypotheses denoted by $H_1,\ldots,H_m$. Let $p_1,\ldots,p_m$ denote the associated raw p-values. Further, let $p_{(1)}<\ldots<p_{(m)}$ denote the ordered p-values and $H_{(1)},\ldots,H_{(m)}$ denote the hypotheses corresponding to the ordered p-values. Finally, let α denote the overall Type I error rate.

The regular Hochberg procedure is based on the following testing algorithm:

- Step 1: If $p_{(m)} > \alpha$, accept $H_{(m)}$ and go to Step 2,
  otherwise reject all null hypotheses and stop.
- Step i = 2,…,m-1: If $p_{(m-i+1)} > \alpha/i$, accept $H_{(m-i+1)}$ and go to Step i+1,
  otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$,
  otherwise reject $H_{(1)}$.

The truncated Hochberg procedure is defined as a convex combination of the Bonferroni procedure and regular Hochberg procedure based on a pre-specified truncation parameter $0 \leq \gamma < 1$ (Dmitrienko, Tamhane and Wiens, 2008 [5]).

The truncated Hochberg procedure is based on the following testing algorithm:

- Step 1: If $p_{(m)} > (\gamma + (1-\gamma)/m)\,\alpha$, accept $H_{(m)}$ and go to Step 2,
  otherwise reject all null hypotheses and stop.
- Step i = 2,…,m-1: If $p_{(m-i+1)} > (\gamma/i + (1-\gamma)/m)\,\alpha$, accept $H_{(m-i+1)}$ and go to Step i+1,
  otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$,
  otherwise reject $H_{(1)}$.

With $\gamma = 0$, the truncated Hochberg procedure simplifies to the Bonferroni procedure and, with $\gamma = 1$, the truncated Hochberg procedure simplifies to the regular Hochberg procedure.

10.4 Sensitivity analyses to address the potential impact of missing data[84]

For the purpose of the sensitivity analyses described in this Appendix, missing data as related to the primary analysis is unobserved follow-up time up until the global rivaroxaban/aspirin outcomes cut-off date. Unobserved follow-up time may occur due to subjects who are non-compliant with study follow-up, for example due to loss of follow-up or premature complete withdrawal of informed consent. Subjects censored administratively at the "global rivaroxaban/aspirin outcomes cut-off date" or censored at time of non-CV death are not contributing missing follow-up time.

In the primary analysis, missing data due to rivaroxaban/aspirin follow-up non-completion before experiencing an unrefuted primary efficacy outcome event is addressed by assuming that such censoring is noninformative/ignorable in a sense like the (missing at random) MAR assumption. That is to say the assumption of its independence from the possibly unobserved time-to-event applies: the possibly unknown true time to the event for a subject is the same regardless of whether or not it is actually observed (or whether censoring occurs or not prior to it) (Zhao, 2014).

Subjects who prematurely discontinue rivaroxaban/aspirin follow-up (rivaroxaban/aspirin follow-up non-completers) may differ systematically from subjects who complete rivaroxaban/aspirin follow-up, thus introducing the possibility of non-ignorable censoring.

Non-ignorable censoring is differential if it leads to bias in the comparison of treatment groups, that is, if the differences in the hazard due to nonignorable censoring in the treatment groups do not "cancel out." (Little et al., 2016).

The sensitivity analyses described in this Appendix to the SAP address the potential impact of missing data on the primary efficacy outcome and follow the elements described by Little et. al. (2016), involving two steps:

1. A descriptive comparison of key baseline characteristics and post-randomization events preceding the end of rivaroxaban/aspirin follow-up to assess whether subjects with missing data differ systematically from subjects who complete the rivaroxaban/aspirin follow-up.
2. A pattern mixture model using multiple imputation techniques to investigate the potential impact of missing data on the primary efficacy analysis if non-ignorable censoring is assumed to be differential.

In addition, the extent of missing data will be described by the fraction of subjects with unobserved rivaroxaban/aspirin follow-up time and the fraction of unobserved rivaroxaban/aspirin follow-up subject-years.

All analyses of the potential impact of missing data will be performed in the ITT analysis set.

10.4.1 Definitions

In the context of missing data sensitivity analyses for the primary efficacy analysis we define, using the terms described in Table 10-2,

[84] Text added as per modification 5 in integrated SAP, Version 4.1.

- a subject with unobserved rivaroxaban/aspirin follow-up time,
  as a rivaroxaban/aspirin follow-up non-completer for whom no unrefuted primary efficacy outcome event was documented and who is alive at the time of censoring,
- a subject's observed rivaroxaban/aspirin follow-up time,
  as the time used in the primary efficacy outcome analysis (time under risk),
- a subject's unobserved rivaroxaban/aspirin follow-up time,
  as the time from censoring to the global rivaroxaban/aspirin outcomes cut-off date for subjects with unobserved rivaroxaban/aspirin follow-up time and zero for subjects with no unobserved rivaroxaban/aspirin follow-up time.

With regard to the extent of "missing data", we define

- the fraction of subjects with unobserved rivaroxaban/aspirin follow-up time,
  as the number of subjects with unobserved rivaroxaban/aspirin follow-up time divided by the number of subjects in the ITT population
- the fraction of missing rivaroxaban/aspirin follow-up subject-years,
  as the sum of the subjects' unobserved rivaroxaban/aspirin follow-up time divided by the sum of the subjects' observed and unobserved rivaroxaban/aspirin follow-up time

These definitions rely on the division of the ITT study population into rivaroxaban/aspirin follow-up completers and rivaroxaban/aspirin follow-up non-completers, see Table 10-2.

Table 10-2. Definition of sensitivity analysis subject characteristics

Subgroups	*Definition*
Rivaroxaban/aspirin follow-up non-completer	Subjects alive for whom • the last contact date during rivaroxaban/aspirin portion of the study is before the global rivaroxaban/aspirin outcomes cut-off date.
Rivaroxaban/aspirin follow-up completer	Subjects for whom • the last contact date during rivaroxaban/aspirin portion of the study is at or after the global rivaroxaban/aspirin outcomes cut-off date • subject died
Rivaroxaban/aspirin study treatment non-completer	Subjects • who are rivaroxaban/aspirin follow-up non-completers and/or • whose date of last rivaroxaban/rivaroxaban placebo or date of last aspirin/aspirin placebo study treatment is before the global rivaroxaban/aspirin outcomes cut-off date or before the subject's death date (whatever comes first)
Rivaroxaban/aspirin study treatment completer	Subjects • who are rivaroxaban/aspirin follow-up completers and • whose date of last rivaroxaban/rivaroxaban placebo and date of last aspirin/aspirin placebo study treatment is at or after the global rivaroxaban/aspirin outcomes cut-off date or identical to the death date

Note: the follow-up definitions from Table 10-2 do not depend on

- premature discontinuation of study medication,

- the experience of an unrefuted primary efficacy outcome (rivaroxaban/aspirin follow-up non-completers may have experienced an unrefuted primary efficacy outcome event before premature discontinuation of their rivaroxaban/aspirin follow-up. However, only rivaroxaban/aspirin follow-up non-completers for whom no unrefuted primary efficacy outcome event is documented might impact the primary analysis due to missing outcome information.) and/or
- the reasons for being a rivaroxaban/aspirin follow-up non-completer, for example "complete withdrawal of informed consent", "lost to follow-up", or "other".

Subjects who died are considered rivaroxaban/aspirin follow-up completers and having no missing outcome information, because subjects who experienced a terminal event cannot be followed-up.

10.4.2 Descriptive comparison of baseline characteristics and post-randomization events

Subjects who prematurely discontinue rivaroxaban/aspirin follow-up (rivaroxaban/aspirin follow-up non-completers) may differ systematically from subjects who complete rivaroxaban/aspirin follow-up. This concern is particularly important if these differences depend on and are different for the study treatment groups.

Therefore descriptive comparisons of key baseline characteristics and post-randomization events preceding end of the rivaroxaban/aspirin follow-up will be conducted. The comparison can provide indirect evidence that the degree of differential nonignorable censoring might be limited.

The analyses will be done for the following subgroups:

- rivaroxaban/aspirin follow-up completers who completed study treatment with rivaroxaban and aspirin
- rivaroxaban/aspirin follow-up completers who prematurely discontinued study treatment with rivaroxaban or aspirin
- rivaroxaban/aspirin follow-up non-completers.

For each subgroup the proportion of subjects with certain baseline characteristics and selected post-randomization events (or means) will be presented by treatment group.

To provide indirect evidence for ignorable censoring, those descriptive comparison will also be conducted for the groups of

- rivaroxaban/aspirin follow-up non-completers for which no unrefuted primary efficacy outcome event was documented
- rivaroxaban/aspirin follow-up completers and non-completers for which an unrefuted primary efficacy outcome event was documented.

In Section 10.4.3, a sensitivity analysis to investigate the potential impact of missing data on the primary efficacy analysis is described. To provide indirect evidence that the selection of the study cohort of subjects from whom information about the unobserved event process is borrowed is reasonable, the descriptive comparison will also include the group of

- subjects who prematurely discontinued any anti-thrombotic study treatment and who are not in the group mentioned above: rivaroxaban/aspirin follow-up non-completers for which no unrefuted primary efficacy outcome event was documented.

Baseline characteristics considered in these analyses are

- Coronary artery disease
- Peripheral artery disease
- CABG surgery (planned within 4-7 days) before randomization
- History of any prior CABG
- Region (North America, Western Europe and AUS/ISR/ZAF, Eastern Europe, Asia Pacific, and South America)
- History of a prior heart failure
- History of (non-lacunar ischemic) stroke
- History of prior MI
- History of prior asymptomatic carotid artery stenosis >= 50%/ revascularization
- Age (<65, 65 years or older)
- Baseline renal function: estimated glomerular filtration rate (eGFR) (<60 mL/min, >=60mL/min)
- Baseline diabetes
- Smoking at baseline

Selected post-randomization events are

- occurrence of an unrefuted major bleeding event
- occurrence of at least one serious adverse event/event of special interest (SAE/ESI)
- hospitalization
- premature discontinuation of blinded rivaroxaban treatment
- premature discontinuation of blinded aspirin treatment.

For the occurrence of major bleedings and SAEs/ESI only events occurring (start date) during the 90 days preceding the unrefuted primary efficacy outcome event or the censoring date relevant for primary analysis will be considered. For subjects observed for less than 90 days after randomization, only the time after randomization will be considered.

10.4.3 Sensitivity analysis

To investigate the potential impact of missing data on the primary efficacy analysis if nonignorable censoring is differential, a sensitivity analysis similar to sensitivity analyses based on pattern-mixture models described by the NRC (NRC 2012) will be employed.

Primary efficacy outcome events in subjects with missing rivaroxaban/aspirin follow-up data will be generated in a three-step process by

(1) defining a cohort (pattern) of subjects from whom information about the unobserved event process is borrowed and estimation of individual hazards from an imputation model

(2) simulation of primary outcome events using individualized hazard estimates at the censoring date to create multiple data sets with imputed data; fitting of the primary analysis model to the imputed data sets; combining the analysis results to generate statistical inference

(3) assessment of the robustness by repetition of step 2 after inflation of the individual hazard estimates in the rivaroxaban treatment groups and determination of the "tipping point".

The subdivision of the ITT set as described in the following steps is illustrated by Figure 10-1.

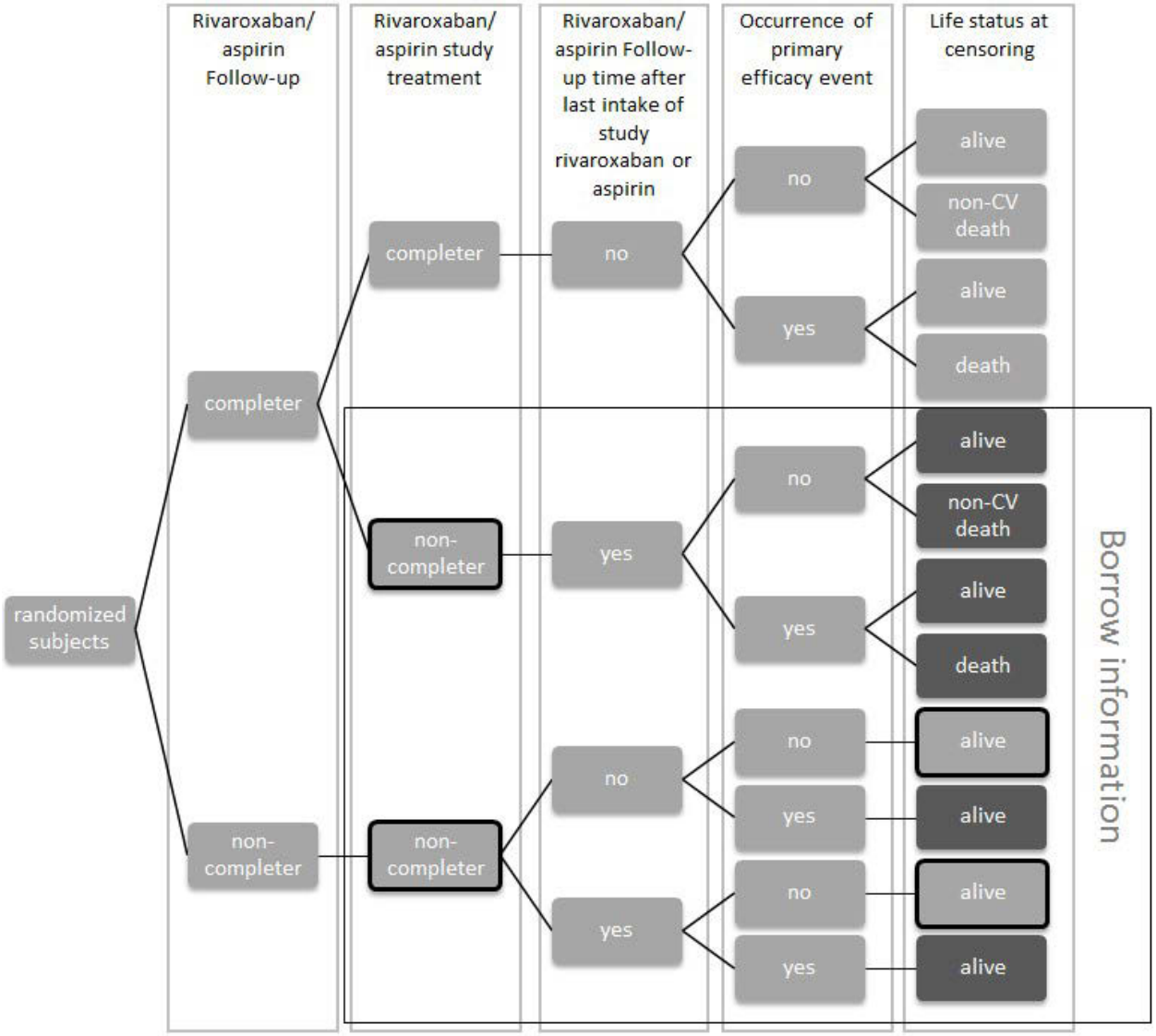

Figure 10-1 Subdivision of ITT set for estimation of individual hazards for imputation

Step 1:

According to the study protocol all subjects are to be followed until the end of the rivaroxaban/aspirin follow-up / end of the study and data on the primary efficacy outcomes are collected irrespective of whether or not a subject is on or off anti-thrombotic treatment. The cohort of subjects who prematurely discontinue any anti-thrombotic study treatment (i.e. either study

rivaroxaban bid and/or study aspirin treatment) will be used for imputation of unobserved follow-up time.

More specifically, for subjects who prematurely discontinued any anti-thrombotic study treatment, a Weibull[85] survival model will be fitted to estimate the individual hazard of a primary outcome event at the last contact date of the rivaroxaban/aspirin portion of the trial. The model will be adjusted for treatment groups (rivaroxaban 2.5 mg bid + aspirin 100 mg od, rivaroxaban 5 mg bid + aspirin placebo od, rivaroxaban placebo + aspirin 100 mg od), stratification factor (not randomized to a proton pump inhibitor; pantoprazole 40 mg od; pantoprazole placebo) and the following baseline covariates:

- CAD and PAD, CAD only, PAD only
- Age (<65, 65 years or older)
- Region (North America, Western Europe, Eastern Europe, Asia Pacific and other, and South America)
- History of a prior heart failure
- History of prior stroke
- History of prior MI

The imputation model will also include a covariate indicating the occurrence of a major bleeding event (post-randomization event), if the bleeding occurred (start date) during the 90 days preceding the unrefuted primary efficacy outcome event or the censoring date relevant for primary analysis:

If the individual hazard for a subject cannot be estimated from the above model due to missing covariates the hazard estimate from a crude model – adjusted for treatment groups and stratification factor only – will be used for this subject (see Section 10.4.4).

Step 2:

For subjects with missing rivaroxaban/aspirin follow-up time who did not experience an unrefuted primary outcome event and were alive at censoring, random variables reflecting a subject's individualized hazard (from step 1) will be simulated using the conditional time to event distribution after the last available rivaroxaban/aspirin follow-up (see Section 10.4.5). If this randomly generated variable has a value less than the elapsed time between the last available rivaroxaban/aspirin follow-up date (exclusive) and the "global rivaroxaban/aspirin outcomes cut-off date" (inclusive), the subject will be treated as having an primary efficacy event occurring at the date of last available rivaroxaban/aspirin follow-up plus the value from the random variable. Otherwise, the subject is re-adjusted to be censored at the "global rivaroxaban/aspirin outcomes cut-off date". Events and time at risk is imputed assuming that no death due to non-CV causes occurs.

Imputed events and event-free time at risk will be added to the observed events and times under risk in the study and the primary efficacy analysis will be repeated: The Cox proportional-hazards models from primary efficacy analysis will be fitted to the imputed data sets. This imputation and

[85] Experience shows that exponential distribution adequately models the survival time. In case of deviating data this approach can easily be extended to Weibull distribution by estimating the scale parameter σ.

analysis of primary outcome events will be repeated 1,000 times. Inferences for combined parameters will be done using multiple imputation rules that reflect imputation uncertainty (see Section 10.4.6).

Step 3:

To assess the robustness of the analyses for deviations from ignorable censoring the last step will be repeated after inflating the hazards for rivaroxaban/aspirin follow-up non-completers in the rivaroxaban groups. The hazards in the control group will not be inflated, that is, for these subjects, rivaroxaban/aspirin follow-up non-completion will be treated as ignorable. Thereafter, the multiple imputation described above will be repeated with the inflated hazards.

The inflation factor be increased stepwise to determine the factor F, for which the upper limit of the 95%-CI for the HR for rivaroxaban 2.5 mg bid + aspirin 100 mg od relative to rivaroxaban placebo + aspirin 100 mg od crosses 1 – the "tipping-point" – and the factor G, for which the upper limit of the 95%-CI for the HR for rivaroxaban 5 mg bid + aspirin placebo od relative to rivaroxaban placebo + aspirin 100 mg od crosses 1.

The following inflation factors will be considered: 10% to 200% increased by 10% steps, 200% to 500% increased by 50% steps and 500% to 1000% increased by 100% steps.

The sensitivity analysis described in this section will be repeated using a Weibull survival model fitted to all randomized subjects and adjusted for treatment groups, stratification factor and the baseline covariates described above.

10.4.4 Parameter estimation

For subjects who prematurely discontinued any anti-thrombotic study treatment, a Weibull survival model will be fitted to estimate the hazard of a primary outcome event at the last contact date in the rivaroxaban/aspirin portion of the trial:

```
PROC LIFEREG DATA = <dataset> OUTEST=<dataset1>;
    MODEL ttevalue*ttecnsr(1) = trtgrpn stratum <covariates> /
                                DISTRIBUTION = weibull INTERCEPT=8 INITIAL=0.2;
    OUTPUT OUT=<dataset2> CDF=cdf XBETA=xbeta;
RUN;
/*
where
dataset  = name of sub-dataset including all ITT subjects who prematurely
discontinued any anti-thrombotic study treatment
dataset1 = SAS data set containing the parameter estimates
dataset2 = SAS data set containing statistics (CDF and x'β) calculated after
fitting the model
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (1 = right-censored, 0 = event)
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
stratumn = variable for PPI stratification factor (three levels)
*/
```

The SAS LIFEREG procedure will be used to model the natural logarithm $w = \log(t)$ of the survival time. The survival function used by SAS has the form

$$S(w) = \exp\left(-\exp\left(\frac{w-\mu}{\sigma}\right)\right),$$

where μ is the location parameter and σ the scale parameter.

Re-parameterization by $\lambda = \exp(\mu)$ and $\beta = 1/\sigma$ results in the survival function S_1 with

$$S(w) = S_1(t) = \exp\left(-\left(\frac{t}{\lambda}\right)^{\beta}\right).$$

The estimated hazard at the last contact date in the rivaroxaban/aspirin portion of the trial will be obtained from the fitted Weibull model, adjusted for treatment and baseline covariates for each subject.

10.4.5 Generation of random variables

Let the survival time T be Weibull distributed, with survival function S_1.

The conditional distribution function of T after the censoring date CD (given that no event was observed before) is given for $s \geq 0$ by

$$G(s) := P(T \leq s + CD | T > CD) = 1 - P(T > s + CD | T > CD) = 1 - \frac{P(T > s + CD)}{P(T > CD)} = 1 - \frac{S_1(s + CD)}{S_1(CD)}.$$

With scale parameter λ and shape parameter β from the underlying Weibull distribution we have

$$G(s) = 1 - \frac{\exp\left(-\left(\frac{s + CD}{\lambda}\right)^{\beta}\right)}{\exp\left(-\left(\frac{CD}{\lambda}\right)^{\beta}\right)},$$

hence

$$G^{-1}(s) = \lambda\left(\left(\frac{CD}{\lambda}\right)^{\beta} - \log(1 - s)\right)^{1/\beta} - CD.$$

If s is generated as a random variable with uniform distribution between 0 and 1, a random variable with distribution function G can be generated using the inverse transformation technique from

$$\lambda\left((CD/\lambda)^{\beta} - \log(1 - rand('uniform'))\right)^{1/\beta} - CD.$$

10.4.6 Analysis of imputed data sets

SAS program code corresponding to the following will be used to get a dataset with hazard ratio estimates from the 1,000 datasets with imputed primary outcome events:

```
ODS LISTING CLOSE;
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(1) = trtgrpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
  ODS OUTPUT PARAMETERESTIMATES=phregparms;
  BY _imputation_;
RUN;
ODS LISTING;
/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (1 = right-censored, 0 = event)
stratumn = variable for PPI stratification factor (three levels)
_imputation_ = variable for the imputation
*/
```

Finally, the results from the 1000 complete datasets will be combined to produce inferential results using the following program code:

```
PROC MIANALYZE PARMS=phregparms;
  MODELEFFECTS trtgrpn;
RUN;
```

A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (COMPASS - Cardiovascular OutcoMes for People using Anticoagulation StrategieS)

Rivaroxaban for the prevention of major cardiovascular events in CAD or PAD (COMPASS)

Bayer study drug	BAY 59-7939 / Rivaroxaban / Xarelto®		
Study purpose:	Comparative combination drug study for new indication SAP documenting analyses for PPI close-out		
Clinical study phase:	III	**Date:**	09 Mai 2018
Study No.:	BAY 59-7939/15786	**Version:**	1.0
Authors:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
ALI	Acute Limb Ischemia
AUS/ISR/ZAF	Australia/Israel/South Africa
bid	Twice daily
CAD	Coronary artery disease
CDB	Clean database
CHD	Coronary heart disease
CI	Confidence interval
CLI	Chronic Limb Ischemia
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
COMPASS LTOLE	COMPASS Long-term Open-Label Extension
CRF	Case report form (either paper or electronic)
CSR	Clinical study report
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
eGFR	estimated glomerular filtration rate
GI	Gastrointestinal
Hb	Hemoglobin
ICH	International Conference on Harmonization
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drugs
od	Once daily
PAD	Peripheral artery disease
PPD	
PPI	Proton pump inhibitor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software

1. Introduction

On February 06, 2017 the Data Safety Monitoring Board (DSMB) for the COMPASS study recommended that the antithrombotic study treatment arms rivaroxaban 2.5 mg bid/aspirin 100 mg od, rivaroxaban 5 mg bid, and aspirin 100 mg od be stopped as soon as an orderly close-out of this portion of the COMPASS trial could be carried out based on results of the first formal interim analysis. The DSMB made no recommendations regarding early termination of the pantoprazole treatment arms of the study. The Steering Committee decided that the pantoprazole study treatment arms will continue.

The database (Clean Database 1, CDB1) underlying the CSR and the publications is based on a cut-off date of July 22, 2017 and, at Bayer, the release date of the first clinical database on August 04, 2017. The results for the antithrombotic randomization have been analyzed and reported in the clinical study report (CSR, PH-39342) of the COMPASS study and multiple scientific publications. The statistical analyses comprise records up to the subjects' rivaroxaban/aspirin washout visits since these data are considered relevant to the antithrombotic study treatment arms.

The close-out of the pantoprazole treatment arms will lead to a second database release (Clean Database 2, CDB2). The primary purpose of the analyses described in this SAP is the

evaluation of outcomes with respect to the pantoprazole randomization. All outcomes with respect to the antithrombotic randomization have been evaluated extensively at CDB1. In addition, it will be explored whether PPI treatment interferes with the effects of rivaroxaban.

Hence, this SAP is to be read in conjunction with the study protocol and the SAP, version 4.1, of the COMPASS study. The SAP describes the planned statistical analyses after CDB2 in the COMPASS study, focusing on analyses with respect to the pantoprazole/placebo randomization.

2. Study Objectives

The main objective for the pantoprazole randomization is

- To determine whether pantoprazole 40 mg od compared with placebo reduces the risk of upper gastrointestinal bleeding, ulceration, or gastrointestinal obstruction or perforation in subjects with CAD or PAD receiving antithrombotic medications.

Other objectives for the pantoprazole randomization are:

- To determine the effect of pantoprazole 40 mg od compared with placebo on the risk of pneumonia, clostridium difficile (C. diff) and other enteric infections, bone fractures, and new diagnosis since randomization of gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease and dementia in subjects with CAD or PAD.
- To determine whether treatment with pantoprazole 40 mg od potentially modifies the effects of antithrombotic treatment on major cardiovascular outcomes or bleeding events. I.e. whether pantoprazole interacts with the treatment effects of rivaroxaban 2.5 mg bid/aspirin 100 mg od vs. aspirin 100 mg od in its impact on outcomes.
- To determine whether treatment with pantoprazole 40 mg od has an effect on premature discontinuation of antithrombotic study treatment.

For further details on study objectives, please refer to integrated SAP, version 4.1.

3. Study Design

For the general study design, please refer to integrated SAP, version 4.1.

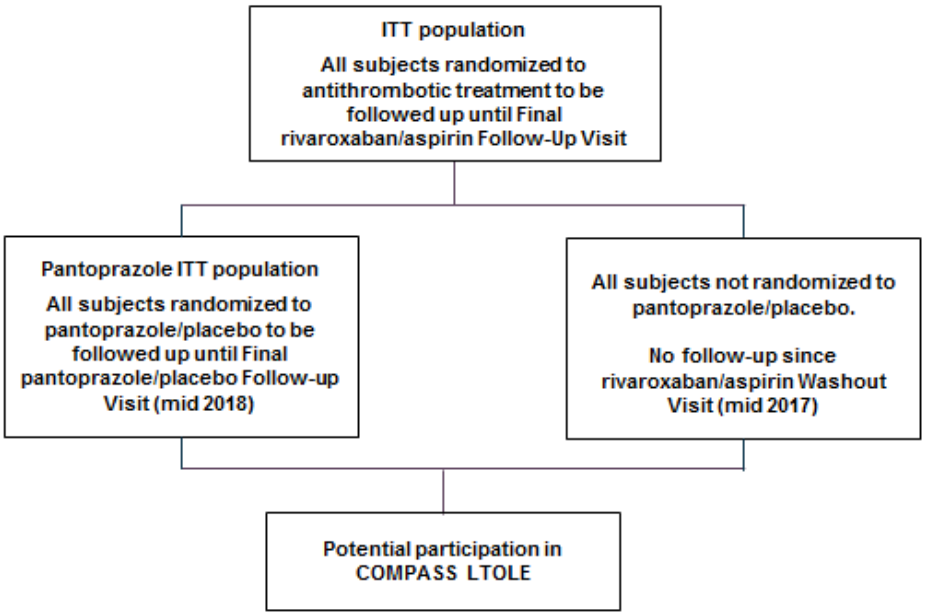
Following the decision of early termination of the antithrombotic treatment arms, all subjects were to stop randomized antithrombotic study treatment with the Final rivaroxaban/aspirin Follow-up Visit (in mid 2017).

- Subjects *randomized to pantoprazole or pantoprazole placebo* were to continue study follow-up as per study protocol up until their Final pantoprazole/placebo Follow-Up Visit (planned for mid 2018).
- Subjects *not randomized to pantoprazole or pantoprazole placebo* were followed-up until their Rivaroxaban/aspirin Washout Visit, i.e. the end of the rivaroxaban/aspirin portion of the trial.

All subjects from COMPASS trial are to be invited to join the COMPASS Long-term Open-Label Extension (COMPASS LTOLE) as long as they continue to meet the COMPASS eligibility criteria plus specific criteria for LTOLE as described in the integrated study

protocol, version 4.0. Initiation visits for the LTOLE study started early 2018 and occur dependent on the approval of the integrated study protocol in the respective country.

Continued antithrombotic therapy between the Final rivaroxaban/aspirin Follow-up Visit and the LTOLE initiation visit was at the discretion of the investigator.



4. General Statistical Considerations

Please also refer to integrated SAP, version 4.1.

4.1 Analysis Sets

The following analysis sets will be used for the analysis of the data from CDB2.

- Intention-to-treat Analysis Set (ITT):
  The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, includes all subjects randomized to antithrombotic study treatment. The ITT set comprises both subjects randomized to pantoprazole/placebo and subjects not randomized to pantoprazole/placebo.
- Pantoprazole ITT Analysis Set (pantoprazole ITT):
  The pantoprazole ITT analysis set comprises all subjects that have been randomized to pantoprazole 40mg or pantoprazole placebo.
- Pantoprazole Safety Analysis Set (pantoprazole SAF):
  The safety analysis set for secondary analyses related to the pantoprazole randomization (pantoprazole safety analysis set) will include all subjects randomized to pantoprazole/placebo who received at least one dose of randomized pantoprazole/placebo medication.
  A subject is considered to have taken at least one dose of pantoprazole/placebo study

medication if the date of permanent discontinuation of pantoprazole/placebo study treatment is later than the randomization date.

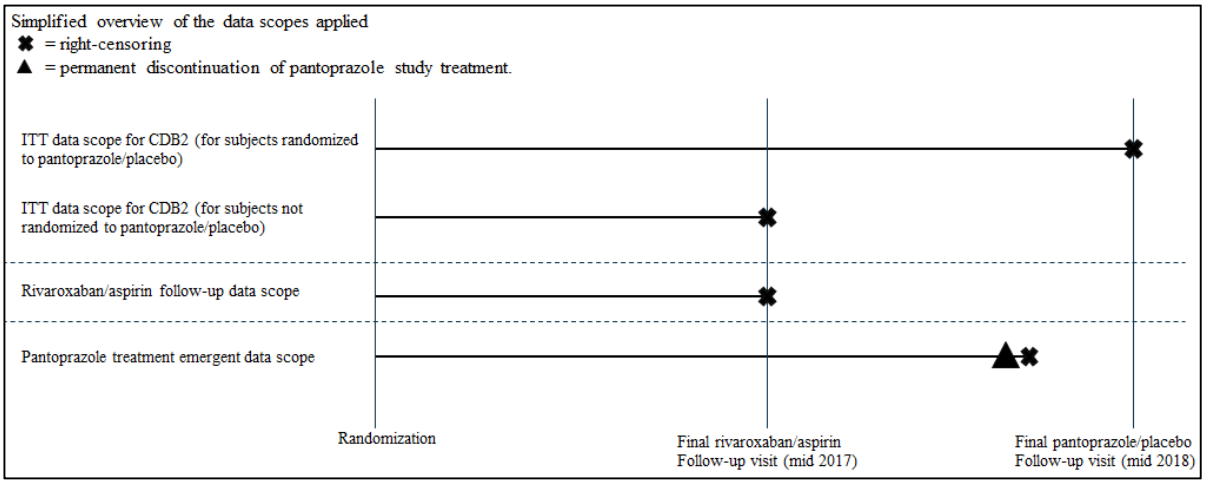
4.2 Data scopes and censoring rules

As per study design, in CDB2 the mean follow-up time of subjects not randomized to pantoprazole or pantoprazole placebo is expected to be significantly shorter than the mean follow-up time of those subjects randomized to pantoprazole/placebo. To reflect this difference, subjects randomized to pantoprazole/placebo and the subjects not randomized to pantoprazole/placebo will be displayed separately to avoid confusion, where applicable.

In general, subjects not randomized to pantoprazole/placebo will only be analyzed up until their Final Rivaroxaban/Aspirin Follow-up Visit. I.e., with respect to the pantoprazole randomization analyses will only consider outcomes up until the Final Rivaroxaban/Aspirin Follow-up Visit for those subjects. Analyses of outcomes with respect to antithrombotic randomization will not be repeated for these subjects, because the analysis has been reported in the CSR (PH-39342) / publications of the COMPASS study.

The following data scopes will be applied in the analyses:

1. ITT data scope for CDB2
2. Rivaroxaban/aspirin follow-up data scope
3. Pantoprazole treatment emergent data scope



4.2.1 ITT data scope for CDB2

The ITT data scope for CDB2 is the primary data scope for analyses of CDB2 data.

For the ITT data scope for CDB2, only outcome events at or after the date of randomization up until Last Follow-up Date (see Section 6 for definition) will be considered for analysis.

For those subjects with documentation of an outcome event within the ITT data scope for CDB2, time (in days) from randomization to the first occurrence of the event will be derived as:

- the date of the subject's first event – the randomization date + 1.

This will constitute an uncensored observation.

For those subjects without documentation of an outcome event within the ITT data scope for CDB2, time (in days) from randomization to the censoring date will be derived as:

- the subject's Last Follow-up Date – the randomization date + 1.

This will constitute a right-censored observation.

4.2.2 Rivaroxaban/aspirin follow-up data scope

The rivaroxaban/aspirin follow-up data scope includes all outcome events from randomization up until the Final rivaroxaban/aspirin Follow-up Visit, for details please refer to the integrated SAP, version 4.1.

4.2.3 Pantoprazole treatment emergent data scope

The pantoprazole treatment emergent data scope includes outcome events from randomization up until two days after permanent discontinuation of pantoprazole study treatment.

It will be used for secondary safety analyses in the pantoprazole safety analysis set. All subjects randomized to pantoprazole/placebo with at least one dose of pantoprazole/placebo study medication and without documentation of an outcome event within the pantoprazole treatment-emergent data scope will be censored at the date of last dose of pantoprazole study treatment + 2 days.

5. Statistical Methodology

All data will be listed and all variables will be summarized by means of descriptive statistics according to their type.

Summaries by randomized study treatment pantoprazole and pantoprazole placebo using appropriate descriptive statistics will be provided overall and/or by antithrombotic treatment group for all study variables including demographic and baseline characteristics. The group not randomized to pantoprazole/placebo due to continuous need for a PPI will be presented separately. No imputation will be applied. Descriptive statistics such as mean, standard deviation, median, quartiles, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Life tables and Kaplan-Meier estimates will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data. Confidence intervals will be provided at a 2-sided level of 95% unless otherwise stated.

5.1 Population characteristics

The structure of the tables describing population characteristics will closely follow the tables provided for CDB1 but comparing randomized pantoprazole treatment with placebo instead of comparing antithrombotic treatment arms.

5.1.1 Sample sizes

Study sample sizes (PPI related analysis sets) will be tabulated overall and by PPI and antithrombotic treatment arms as follows:

- Study sample sizes by region and country
- Study sample sizes by country and site

5.1.2 Subject disposition – Overview/Details at visits

Subject disposition will be presented with primary focus on the PPI related part of the study.

5.1.3 Visit and study drug adherence

The following will be tabulated overall and by PPI treatment arm:

- Number of subjects and reasons for premature permanent discontinuation of study pantoprazole medication
- Number of subjects and reasons for premature permanent discontinuation of study rivaroxaban/aspirin medication
- Number of subjects and reasons for premature permanent discontinuation of study follow up, i.e. consent withdrawn or lost to follow-up.

For CSR purposes, incidences for permanent discontinuation of the double-blinded pantoprazole study drug and of the follow-up period will be provided by randomized pantoprazole study treatment groups, based on the case report form data. In addition, incidences for permanent discontinuation of the double-blinded pantoprazole study drug and of the follow-up period will be provided by PPI treatment groups.

Kaplan-Meier estimates will be used to present

- time to the date of last dose of pantoprazole study treatment (calculated as days from randomization), and,
- time to last follow-up date

all calculated as days from randomization, by randomized pantoprazole treatment group.

Other details regarding visit adherence (e.g., visit completed in person, by telephone, through third party) and completion as well as study drug adherence collected via CRFs will be summarized using frequency tables by visit and randomized pantoprazole treatment group.

Potential pantoprazole effect on premature discontinuation of antithrombotic treatment

A time-to-event variable “Time to premature discontinuation of rivaroxaban/aspirin study treatment” will be defined as follows:

For those subjects with documentation of premature discontinuation of either rivaroxaban/placebo or aspirin/placebo treatment before the common outcomes cut-off date used in CDB1, February 06, 2017, time (in days) from randomization to the occurrence of the event will be derived as:

- the date of permanent treatment discontinuation – the randomization date + 1.

This will constitute an uncensored observation.

For those subjects without documentation of premature discontinuation of either rivaroxaban/placebo or aspirin/placebo treatment before the common outcomes cut-off date used in CDB1, February 06, 2017, time (in days) from randomization to the censoring date will be derived as:

- common outcomes cut-off date – the randomization date + 1.

This will constitute a right-censored observation.

A potential effect of pantoprazole treatment on premature discontinuation of antithrombotic treatment will be analyzed in the pantoprazole ITT analysis set using a log-rank test and a Cox proportional hazards model.

In the unlikely event that the risk to prematurely discontinue antithrombotic treatment is significantly reduced in the pantoprazole treatment group, further analyses will be performed to explore this finding. This exploration may include a time-dependent Cox model investigating the effect of premature discontinuation of antithrombotic treatment on major cardiovascular outcomes.

5.1.4 Protocol Deviations

No per protocol analysis set will be defined in this study. The number of subjects with major protocol deviations according to the CRF will be summarized by randomized pantoprazole and antithrombotic treatment groups, and overall. The types of deviations are described in the Data Management Plan.

5.1.5 Medical History

Medical history will be evaluated by frequency tables in the ITT analysis set (and, for CSR purposes, the pantoprazole safety set) by pantoprazole treatment groups, showing the number of subjects with medical history findings (i.e., listed conditions of previous diagnoses, diseases, or surgeries based on the CRF).

5.1.6 Demographics

Demographic data will be evaluated descriptively for the ITT analysis set (and, for CSR purposes, the pantoprazole safety set) by PPI and antithrombotic study treatment groups, and overall.

Descriptive statistics (such as mean, standard deviation, median, quartiles, minimum and maximum) will be provided for continuous variables such as

- Age [years]
- Height [cm]
- Weight [kg]
- Waist and hip circumference [cm]
- Body mass index [kg/m²]

Counts and (appropriate) percentages will be provided for categorical variables such as

- Gender
- Ethnic group and ethnicity/race
- Tobacco use

5.1.7 Prior and Concomitant Medication

Frequency tables by pantoprazole treatment group and overall, will be used to summarize the number of subjects with

- prior relevant antiplatelet agents and anticoagulant reported by the subject at the Screening/Run-in Visit
- relevant concomitant medications at randomization (non-study medications taken regularly for at least 1 month at the time of the randomization visit), for CDB2 defined as: non-study proton pump inhibitor and Non-steroidal anti-inflammatory drugs (NSAIDs).
- non-study antithrombotic therapy (antiplatelet agents and anticoagulant) reported at the scheduled follow-up visits
- relevant concomitant medications recorded at a Follow-Up Visit 2 years after randomization
- relevant concomitant medications recorded at the Final Follow-Up Visit(s).

5.2 Efficacy

In general, due to the early discontinuation of antithrombotic treatment arms, subjects randomized to pantoprazole 40 mg or placebo on the one hand and subjects not randomized to pantoprazole/placebo but randomized to antithrombotic treatment only on the other hand, are suspected to differ in time under observation systematically. The following analyses attempt to take this bias into account.

5.2.1 Efficacy Variables for the Pantoprazole Randomization

The main efficacy variable for the pantoprazole randomization is the time (in days) from randomization to the first occurrence of an unrefuted GI outcome event, which is the composite of the following outcomes:

- Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
- Overt upper gastrointestinal bleeding of unknown origin
- Bleeding of presumed occult upper gastrointestinal tract origin with documented decrease in Hb of 2 g/dL
- Symptomatic gastroduodenal ulcer
- Gastrointestinal pain with underlying multiple gastroduodenal erosions
- Upper GI obstruction/perforation.

Details by individual components will also be presented.

Further outcomes of interest for the pantoprazole randomization, which will also be evaluated as time-to-event variables, are:

- GI bleeding, defined as the composite of the first three components above:
    - Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
    - Overt upper gastrointestinal bleeding of unknown origin

- Bleeding of presumed occult upper gastrointestinal tract origin with documented decrease in Hb of 2 g/dL

5.2.2 Efficacy Outcomes for the Antithrombotic Randomization by Pantoprazole Treatment Groups

Other efficacy outcomes of interest are the unrefuted occurrences of outcomes which had been defined in the clinical study protocol for the objectives of the antithrombotic randomization, i.e.:

- MI, stroke, or CV death
  - MI
  - Stroke
  - CV death (and its cause)
- MI, ischemic stroke, ALI, CHD death
  - Ischemic Stroke
  - ALI
  - CHD death
- MI, ischemic stroke, ALI, CV death
- All-cause mortality
  - Non-CV death (and its cause)
- Major adverse limb event
  - ALI
  - Chronic limb ischemia
- New diagnosis of cancer (including subtypes)
- Recurrence of cancer
- Hospitalization
  - Hospitalization for CV reasons

Other outcomes of interest for the antithrombotic randomization related to cognition and function will be reported separately.

5.2.3 Statistical Analysis for the Pantoprazole Randomization

The following analyses are to be conducted for the efficacy variables of the pantoprazole randomization as defined in section 5.2.1 separately for the ITT data scope for CDB2

- in the pantoprazole ITT analysis set and
- in the subjects not randomized to pantoprazole/placebo.

Descriptive statistics for pantoprazole outcomes

For outcomes relevant for the pantoprazole/placebo randomization, the number of subjects with event, crude incidences and incidence rates will be depicted in the following manner:

Subjects randomized to pantoprazole 40 mg or placebo on the one hand and subjects not randomized to pantoprazole/placebo on the other hand are suspected to differ in time under observation systematically. Hence, those two groups will be displayed in separate tables to avoid potential confusion arising from erroneously comparing these groups, see the following example:

The following tables will be repeated for the antithrombotic treatment arms <xxx>:

- **Overall and,**
- **for CSR purposes only, by antithrombotic treatment arm**
  - **Randomized to Rivaroxaban 2.5 mg bid, Aspirin 100 mg od**
  - **Randomized to Rivaroxaban 5 mg**
  - **Randomized to Aspirin 100 mg od**

Table: Number of subjects with <event> in ITT data scope for CDB2 (pantoprazole ITT analysis set)

Antithrombotic treatment arm: <xxx>

	Pantoprazole 40 mg od N=xxx (100%)		Pantoprazole placebo od N=xxx (100%)		Total N= xxx (100%)	
	N (%)	N/100 p-yrs (95% CI)	N (%)	N/100 p-yrs (95% CI)	N (%)	N/100 p-yrs (95% CI)
<event>	xx (x.x%)	x.xx (x.xx;x.xx)	xx (x.x%)	x.xx (x.xx;x.xx)	xx (x.x%)	x.xx (x.xx;x.xx)

- Only events that occurred during ITT data scope for CDB2 are taken into account.

Table: Number of subjects with <event> in ITT data scope for CDB2 (ITT analysis set)

Antithrombotic treatment arm: <xxx>

	Not randomized to pantoprazole/placebo N=xxx (100%)	
	N (%)	N/100 p-yrs (95% CI)
<event>	xx (x.x%)	x.xx (x.xx;x.xx)

- Only events that occurred during ITT data scope for CDB2 are taken into account.

Inferential statistics for pantoprazole outcomes

The statistical analysis of the outcome for the pantoprazole randomization will be based on the intention-to-treat principle and will include all subjects randomized to receive pantoprazole 40 mg od or pantoprazole placebo.

The null hypothesis $H_{0;panto40}$ stating that

> "there is no difference between the pantoprazole treatment and control group in the probability of the outcome for all time points"

will be tested against the alternative hypothesis $H_{1;panto40}$ stating that

> "there is a difference between the two groups in the probability of the outcome for at least one time point".

Stratified log-rank test and Kaplan-Meier estimates

Statistical testing will be performed by a comparison of the "survival functions" $S(t)$, i.e., the probability that "time from randomization to the first occurrence of the outcome" is > t, for a time t relative to randomization. The comparison will be performed using a log-rank test stratified by antithrombotic study treatment (three strata levels: rivaroxaban 2.5 mg bid + aspirin 100 mg od; rivaroxaban 5 mg bid + aspirin placebo; rivaroxaban placebo + aspirin 100 mg od), conducted at the 2-sided 5% type I error level.

Kaplan-Meier estimates of cumulative risk functions and Nelson-Aalen estimates of the cumulative hazard functions will be provided to evaluate the timing of event occurrence in the two proton pump inhibitor study groups and the consistency of the treatment effect for all time points (the two survival curves do not cross).

To derive the log-rank Z test statistic and the variance V of the log-rank statistics, SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = <dataset> ALPHA = 0.05 METHOD = KM NELSON;
STRATA stratumn / GROUP = ppi1grpn TEST = (LOGRANK);
TIME ttevalue * ttecnsr(1);
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to pantoprazole
           treatment groups: pantoprazole 40 mg/pantoprazole placebo
ppi1grpn = variable coding randomized pantoprazole treatment group (0 = pantoprazole
           placebo, 1 = pantoprazole 40 mg)
ttevalue = time to first occurrence of pantoprazole outcome event
ttecnsr  = censoring index (1 = right-censored, 0 = event)
stratumn = variable for antithrombotic stratification factor (three levels)
*/
```

Cox proportional hazards model

Hazard ratios and corresponding 2-sided 95% confidence intervals will be estimated based on a Cox proportional hazards model stratified by antithrombotic therapy study group. Censoring will be assumed independent of the treatment group assignment.

For the analysis of the outcome for the pantoprazole randomization in this study, the hazard function h(t) is the chance that an individual experiences an event of the outcome of the pantoprazole randomization in the next instant in time, given that the individual has not had such an event up to time t. For example, for the comparison of pantoprazole 40 mg od to pantoprazole placebo (control), the corresponding stratified Cox proportional hazards model can be described by the following equation:

$$h_k(t,x_i) = h_{0k}(t) \exp(\beta x_i),$$

where

$h_k(.)$ hazard function for primary efficacy outcome for stratum k, k = 1,2,3 (k represents randomized antithrombotic study treatment stratification factor), as a function of time and subject's covariates

$h_{0k}(.)$ unspecified underlying baseline hazard function for primary efficacy outcome per stratum k; hazard of an individual with $x_i = 0$

t time (in days) relative to the randomization date

x_i PPI treatment group of subject i
(0 corresponds to "pantoprazole placebo (control)" and
1 corresponds to "pantoprazole 40 mg od")

β unknown parameter (to be estimated); hazard ratio = exp(β)

SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(1) = ppi1grpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           pantoprazole 40 mg or pantoprazole placebo study treatment
ppi1grpn  = variable coding randomized pantoprazole treatment group
           (0 = pantoprazole placebo, 1 = pantoprazole 40 mg treatment)
ttevalue = time to first occurrence of pantoprazole outcome event
ttecnsr  = censoring index (1 = right-censored, 0 = event)
stratumn = variable for randomized antithrombotic study treatment
           stratification factor (three levels)
*/
```

Additional procedure options controlling the output may be added to the program codes.

Plausibility of proportional hazards assumption

The plausibility of the proportional hazards assumption will be assessed by visually examining both the plot of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log time for evidence of non-parallelism and the smoothed plot of the scaled Schoenfeld residuals to directly visualize the log hazard ratio (Grambsch and Therneau, 1994), for each stratum separately, and by including a time-treatment interaction term in the Cox model (time log transformed). The significance of the interaction will be tested at the 5% type I error level. If the interaction is significant and there is strong evidence of non-proportionality from the plots, time-dependent hazard ratios will be estimated with the model that includes the interaction term.

Interaction between pantoprazole and antithrombotic treatment groups

The randomized antithrombotic treatment was to be stopped with the Final rivaroxaban/aspirin Follow-up Visit. Hence, the analysis of joint effects and interaction between antithrombotic and pantoprazole treatments on the pantoprazole outcome as described below will be based on the rivaroxaban/aspirin follow-up data scope, including events from randomization up until Final rivaroxaban/aspirin Follow-up Visit.

The joint effect and interaction between the antithrombotic and pantoprazole study groups on the pantoprazole outcome will be explored based on the intention-to-treat principle in subjects randomized to receive pantoprazole 40 mg od or pantoprazole placebo. The analysis will use two separate Cox proportional hazards models, one for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od, and one for the

comparison of rivaroxaban 5 mg bid+ aspirin placebo vs. rivaroxaban placebo + aspirin 100 mg od. The models will include:

- a covariate for the effect of the considered rivaroxaban-based treatment group vs. the aspirin-control group,
- a covariate for the effect of pantoprazole 40 mg od treatment group vs. pantoprazole placebo-control group,
- an interaction term of these two factors.

Therefore, the Cox proportional hazards model (e.g., for the comparison of rivaroxaban 2.5 mg bid + aspirin 100 mg od vs. rivaroxaban placebo + aspirin 100 mg od) can be described by the following equation:

$$h(t,x_{1i},x_{2i}) = h_0(t) \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_{12} x_{1i} x_{2i}),$$

where

$h(.)$ hazard function for pantoprazole outcome as a function of time and subject's covariates

$h_0(.)$ unspecified underlying baseline hazard function for pantoprazole outcome

t time (in days) relative to the randomization date

x_{1i} antithrombotic treatment group of subject i
(0 corresponds to "rivaroxaban placebo + aspirin 100 mg od (control)" and
1 corresponds to "rivaroxaban 2.5 mg bid + aspirin 100 mg od")

x_{2i} pantoprazole group of subject i
(0 corresponds to "pantoprazole placebo-control group" and
1 corresponds to "pantoprazole 40 mg od treatment group")

$\beta_1, \beta_2, \beta_{12}$ unknown parameters (to be estimated)

SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn ppi1grpn trtgrpn*ppi1grpn /
                                RL TIES=EFRON ALPHA=0.05;
RUN;

/*
where
dataset  = name of sub-dataset including all ITT subjects randomized to
           respective rivaroxaban treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = control group, 1 = rivaroxaban 2.5 mg + aspirin 100 mg)
ppi1grpn = variable coding randomized pantoprazole treatment group
           (0 = pantoprazole placebo, 1 = pantoprazole 40 mg treatment)
ttevalue = time to first occurrence of pantoprazole outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
*/
```

Additional analyses

Additional exploratory analyses will include, e.g., a comparison of subjects of the ITT analysis set who were not randomized to receive pantoprazole 40 mg od or pantoprazole placebo with subjects randomized to pantoprazole placebo with regard to the pantoprazole outcome during the Rivaroxaban/aspirin follow-up data scope.

5.2.4 Further Statistical Analysis for the Pantoprazole Randomization

Furthermore, the following additional statistical analyses will be provided:

- For the components of the unrefuted GI outcome, descriptive statistics and Kaplan-Meier estimates will be provided and the components will be analyzed using the stratified log-rank test and the Cox proportional hazards model as described above in the pantoprazole ITT analysis set for the ITT data scope for CDB2.
- For the unrefuted GI outcome and it components, descriptive statistics will be provided and an analysis using the stratified log-rank test and the Cox proportional hazards model as described above will be repeated in the pantoprazole safety set for the pantoprazole treatment emergent data scope.

5.2.5 Subgroup Analyses

Subgroup analyses for comparison of pantoprazole 40 mg and pantoprazole placebo will be performed based on the pantoprazole ITT analysis set for the ITT data scope for CBD2.

Homogeneity of treatment effect (i.e., the effect of pantoprazole study treatment on the pantoprazole outcome) will be examined for the following subgroup variables, where important subgroups are distinguished from “other” subgroups that are examined to assess the consistency of a treatment effect:

Important subgroups

- Antithrombotic treatment group (rivaroxaban 2.5mg, rivaroxaban 5mg, aspirin 100mg)
- Coronary artery disease (yes, no)
- Peripheral artery disease (yes, no)

Other subgroups

- Region
  - North America, Western Europe and AUS/ISR/ZAF, Eastern Europe, Asia Pacific, and South America, see SAP, version 4.1, Appendix 10.1
  - US, non-US
- Sex (male, female)
- Age
  - Categories 1: <55, 55 to <65, 65 to 75, >75 years
  - Categories 2: < 65, ≥ 65 to < 75, ≥ 75 years
- Race (White or Caucasian, Black or African American, Asian, other)
- Body weight at baseline (≤ 60 kg, > 60 kg)
- Baseline renal function
  - estimated glomerular filtration rate (eGFR) categories 1: <60, ≥60 mL/min

  - eGFR categories 2: < 15, 15 to < 30, 30 to < 60, ≥ 60 mL/min
  - eGFR categories 3: < 30, 30 to 50, >50 to 80 ml/min, >80 ml/min
- Smoking status
  - Tobacco use at baseline (yes, no)
  - History of tobacco use (yes, no)
- Baseline diabetes (yes, no)
- History of peptic ulcer (yes, no)
- History of Helicobacter pylori (yes, no, unknown)
- Baseline NSAID use (yes, no)

Additional subgroup analyses, if identified, can be specified. The pre-specified categories may be collapsed if the number of events is too small for some subgroups. In addition to analyses of the subgroups listed above, analyses for the Asian populations, especially Chinese and Japanese subjects, will be performed as required and presented in separate reports.

Homogeneity of study treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective stratified Cox proportional hazards model used in the main analysis.

As the number of subgroup analyses may be large, the probability of observing at least one statistically significant but spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus any significant interactions in the analysis of primary outcomes will be interpreted as "flags" to prompt further investigation.

No interactions with any of the subgroup variables are expected. Furthermore, in the analysis of all outcomes, if the interaction term is significant at the 5% type I error level, the likelihood ratio test proposed by Gail and Simon (1985) will be performed to test the hypothesis that there is no crossover or qualitative interaction at the 1% type I error level (H_0: The direction of treatment effect is the same for all levels of a subgroup variable vs. H_1: The direction of treatment effect is different for at least one level of a subgroup variable). As was shown by Li et al (2007), the probability of observing the treatment effect in the opposite direction to the true overall treatment effect for at least one subgroup level is not negligible. The contributing factors may be small subgroup sizes, imbalance of randomized groups within the subgroups, and small true overall treatment effect.

Following the test of interaction, hazard ratios with 2-sided 95% confidence intervals for the treatment effect will be estimated separately within each level of a subgroup variable using the stratified Cox proportional hazards models that were used in the main analyses of study outcomes.

5.2.6 Potential Modification of Rivaroxaban Treatment Effect by Pantoprazole

The results of the Cox proportional hazards model including the effects of antithrombotic treatment, pantoprazole treatment, and the interaction of those have been reported for selected outcomes based on CDB1 to exclude an interaction effect between antithrombotic and pantoprazole treatment.

To further investigate if pantoprazole treatment has the potential to modify the rivaroxaban treatment effect on the following unrefuted outcomes

- Primary efficacy outcome
- Composite of MI, ischemic stroke, and CV death
- Secondary efficacy outcome
- Modified ISTH major bleeding
- Modified ISTH major bleeding in gastrointestinal tract
- GI bleeding (composite of the first three components of the GI outcome referring to upper GI bleeding),

these outcomes will be evaluated for the ITT analysis set by antithrombotic treatment groups in the rivaroxaban/aspirin follow-up data scope by depicting

- the number of subjects with event, crude incidences, incidence rates and Kaplan-Meier estimates in
    - the ITT analysis set
    - the pantoprazole treatment groups
        - pantoprazole 40mg od
        - pantoprazole placebo od
        - not randomized to pantoprazole/placebo
- the assessment of homogeneity of rivaroxaban treatment effect by the pantoprazole treatment groups (including subgroup-interaction p-value)
- forest plots for the above.

5.2.7 Analysis of Efficacy Outcomes for Antithrombotic Randomization by Pantoprazole Treatment Groups

Subjects not randomized to pantoprazole/placebo were not followed up from the termination of the antithrombotic portion of the COMPASS study until the initiation of COMPASS LTOLE. Only subjects of the pantoprazole ITT analysis set were to be followed up until the Final pantoprazole/placebo Follow-up Visit, mainly to evaluate pantoprazole related outcomes.

Efficacy outcomes defined to analyze the objectives of the antithrombotic randomization in ITT data scope for CDB2 (i.e., up until the Final pantoprazole/placebo Follow-up Visit) will be reported by means of frequency tables only based on the pantoprazole ITT analysis set, by pantoprazole treatment groups, as suggested in the following example.

Table: Number of subjects with primary efficacy event and its components in ITT data scope for CDB2 (pantoprazole ITT analysis set)

	Pantoprazole 40 mg od N=xxxx (100%)	Pantoprazole placebo od N=xxxx (100%)	Total N= xxxx (100%)
MI, stroke, or CV death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

MI	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Stroke	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
CV death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Footnotes:
- Only events that occurred in ITT data scope for CDB2 are taken into account.
- The events presented were efficacy events with respect to antithrombotic randomization. Antithrombotic study medication was to be stopped with Final Rivaroxaban/Aspirin Follow-up Visit. Hence, the randomized antithrombotic study medication was not to be taken for about one year during pantoprazole/placebo follow-up.

5.3 Pharmacokinetics/Pharmacodynamics

Not applicable.

5.4 Safety

5.4.1 Safety Outcome Events for the Antithrombotic Randomization

Safety outcomes defined to analyze the objectives of the antithrombotic randomization in ITT data scope for CDB2 will be reported by means of frequency tables only based on the pantoprazole ITT analysis set, by pantoprazole treatment groups, as described in Section 5.2.7. These tables will be provided similarly to but separate from summaries of AE data.

The following safety events and their composites will be tabularized:

- Modified ISTH major bleeding
  - Fatal
  - Critical organ bleeding (non-fatal)
  - Requiring re-operation (non-fatal and non- critical organ)
  - Hospitalization (non-fatal, non-critical organ, not leading to re-operation)
  - Hospitalization where admission date < discharge date
  - Hospitalization where admission date = discharge date
  - Gastrointestinal
  - Gastrointestinal (excl. oral cavity and esophagus)
  - Intracranial
- Minor bleeding
- Modified ISTH major bleeding by bleeding site

5.4.2 Events of Special Interest for the Pantoprazole Randomization

Other (adverse) events of special interest with respect to the pantoprazole/placebo randomization are

- Pneumonia
- Clostridium difficile infection
- Other enteric infections
- Fracture
- Gastric atrophy

- Chronic kidney disease
- Diabetes
- Chronic obstructive lung disease
- Dementia.

The number and crude incidence of subjects with such events since informed consent (as the CRF suggests) will be summarized. The binary response variables will be evaluated with logistic regression as suggested by the following SAS code:

```
PROC LOGISTIC DATA = <dataset>;
CLASS trtgrpn stratumn;
MODEL outcome (event='1') = trtgrpn / CLODDS= WALD CLPARM= WALD ;
STRATA stratumn;
RUN;

/*
where
dataset = name of sub-dataset including Pantoprazole ITT subjects (those
      subjects randomized to pantoprazole/placebo)
trtgrpn = variable coding randomized pantoprazole treatment group
      (0 = Pantoprazole placebo, 1 = Pantoprazole)
outcome = event indicator (0 = no event, 1 = event)
stratumn = variable for antithrombotic stratification factor (three levels)
*/
```

5.4.3 Adverse Events

Summaries of reported adverse events will be provided based on

- the pantoprazole ITT analysis set using the ITT data scope for CDB2 and,
- for CSR purpose only, the pantoprazole safety analysis set and the pantoprazole treatment emergent data scope

as outlined in Section 4.2. The remaining principles of adverse event analyses will be applied as specified in the SAP, version 4.1.

5.4.4 Death

Please refer to Section 5.4.1.

5.4.5 Pregnancies

Please refer to SAP, version 4.1.

5.4.6 Vital Signs

Please refer to SAP, version 4.1.

5.4.7 Clinical Laboratory Tests

Please refer to SAP, version 4.1.

5.5 Analysis of COMPASS MIND Study

Will be reported separately.

6. Definitions

Pantoprazole ITT analysis set	The pantoprazole ITT analysis set comprises all subjects that have been randomized to pantoprazole 40mg or pantoprazole placebo.
Final pantoprazole/placebo Follow-up Visit	Final visit at the end of the pantoprazole/placebo follow-up of the COMPASS trial
Pantoprazole/placebo Washout Visit	For subjects who participate in COMPASS in countries that have not yet approved the protocol amendment no. 11 forming integrated protocol version 4.0, an End of Washout Telephone Visit (Washout Visit) is envisaged 30 days post Final pantoprazole/placebo Follow-up Visit.
Last rivaroxaban/aspirin Follow-up Date	If consent was not withdrawn: Last rivaroxaban/aspirin Follow-up Date = first of • date of death (if applicable) • date of completed Final rivaroxaban/aspirin Follow-up visit (if applicable) • max (dates of visits completed, event dates). If consent was withdrawn: Last rivaroxaban/aspirin Follow-up Date = first of • max (date of death, date of withdrawal, date of confirmed alive) • date of completed Final rivaroxaban/aspirin Follow-up visit (if applicable).
Last pantoprazole/placebo Follow-up Date	If consent was not withdrawn: Last pantoprazole/placebo Follow-up Date = first of • date of death (if applicable) • date of completed Final pantoprazole/placebo Follow-up visit (if applicable)

	• max (dates of visits completed, event dates). If consent was withdrawn: <u>Last pantoprazole/placebo Follow-up Date</u> = first of • max (date of death, date of withdrawal, date of confirmed alive) • date of completed Final pantoprazole/placebo Follow-up visit (if applicable).
Last Follow-up Date	If subject is in pantoprazole ITT set: <u>Last Follow-up Date</u> = Last pantoprazole/placebo Follow-up Date If subject is not randomized to pantoprazole/placebo: <u>Last Follow-up Date</u> = Last rivaroxaban/aspirin Follow-up Date

7. Document History and Changes in the Planned Statistical Analysis

8. References

CSR, Clinical Study Report of the COMPASS study, PH-39342, October 16, 2017.

Gail M., Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics,1985; 41:361-372.

Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika, 1994; 81(3):515-526.

Li Z., Chuang-Stein C, Hoseyni C. The probability of observing negative subgroup results when the treatment effect is positive and homogeneous across all subgroups. Drug Information Journal, 2007; 41:47-56.

SAP, version 4.1. Integrated Statistical Analysis Plan for the COMPASS study, March 31, 2017.

A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (COMPASS - Cardiovascular OutcoMes for People using Anticoagulation StrategieS)

Rivaroxaban for the prevention of major cardiovascular events in CAD or PAD (COMPASS)

Bayer study drug	BAY 59-7939 / Rivaroxaban / Xarelto®		
Study purpose:	Summary of the long term open label extension part of COMPASS		
Clinical study phase:	III	**Date:**	21 JUL 2021
Study No.:	BAY 59-7939/15786	**Version:**	2.0
Authors:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

AE	Adverse event
AUS/ISR/ZAF	Australia/Israel/South Africa
bid	Twice daily
CAD	Coronary artery disease
CDB	Clean database
CHD	Coronary heart disease
CI	Confidence interval
CLI	Chronic Limb Ischemia
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
COMPASS LTOLE	COMPASS Long-term Open-Label Extension
CRF	Case report form (either paper or electronic)
CSR	Clinical study report
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
eGFR	estimated glomerular filtration rate
GI	Gastrointestinal
Hb	Hemoglobin
ICH	International Conference on Harmonization
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
LTOLE	Long-Term Open-Label Extension (= COMPASS LTOLE)
MI	Myocardial infarction
od	Once daily
PAD	Peripheral artery disease
PPD	
PPI	Proton pump inhibitor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software

1. Introduction

The COMPASS study is a randomized double-blind trial utilizing a 3 x 2 partial factorial design evaluating the efficacy and safety of:

- rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (od) versus aspirin 100 mg od and
- rivaroxaban 5 mg bid versus aspirin 100 mg od

for the prevention of myocardial infarction, stroke, and cardiovascular death in patients with established CAD or PAD who are receiving standard prevention therapies. Details about the study, as well as the already specified and conducted analyses are described in the integrated clinical study protocol, Version 4.0, dated 12 September 2017, the integrated SAP, Version 4.1, dated 31 March 2017 and the SAP for PPI-specific analyses, Version 1.0, dated 09 May 2018.

On February 06, 2017 the Data Safety Monitoring Board (DSMB) for the COMPASS study recommended that the antithrombotic study treatment arms rivaroxaban 2.5 mg bid/aspirin 100 mg od, rivaroxaban 5 mg bid, and aspirin 100 mg od be stopped as soon as an orderly close-out of this portion of the COMPASS trial could be carried out based on results of the first formal interim analysis. The DSMB made no recommendations regarding early termination of the pantoprazole treatment arms of the study. The Steering Committee decided that the pantoprazole study treatment arms would continue.

The database (Clean Database 1, CDB1) underlying the CSR and the main publications is based on a cut-off date of July 22, 2017 and, at Bayer, the release date of the first clinical database on August 04, 2017. The results for the antithrombotic randomization have been analyzed and reported in the clinical study report (CSR, PH-39342) of the COMPASS study and multiple scientific publications. The corresponding statistical analyses comprise information up to the subjects' rivaroxaban/aspirin washout visits since these data are considered relevant to the antithrombotic study treatment arms.

Based on a further data cut-off on August 31, 2018 a second Clean Database (CDB2) has been released on September 21, 2018 underlying the CSR addendum (PH-40183) and summarizing the results focusing on the pantoprazole randomization.

After the early stop of the antithrombotic study treatment in the COMPASS study, the sponsor made rivaroxaban 2.5 mg bis + aspirin 100 mg od available early for COMPASS trial subjects as part of a Long-Term Open-Label Extension (COMPASS LTOLE; short: LTOLE). Subjects who participated in the COMPASS study were invited to join LTOLE, and eligible subjects who agreed to participate were treated with the combination of rivaroxaban 2.5 mg bid/aspirin 100 mg od.

The primary purpose of the analyses described in this SAP is the evaluation of relevant outcomes in COMPASS that occurred during the LTOLE part of the study.

Hence, this SAP is to be read in conjunction with the study protocol and the SAPs mentioned above. The COMPASS study will be concluded with the completion of LTOLE.

2. Study Objectives

Objective for Long-Term Open-Label Extension

- The objective of LTOLE is to make rivaroxaban 2.5 mg bid + aspirin 100 mg od available to COMPASS trial subjects until the treatment is commercially available or for approximately 3 years from regulatory approval of LTOLE in a country, whichever comes first.

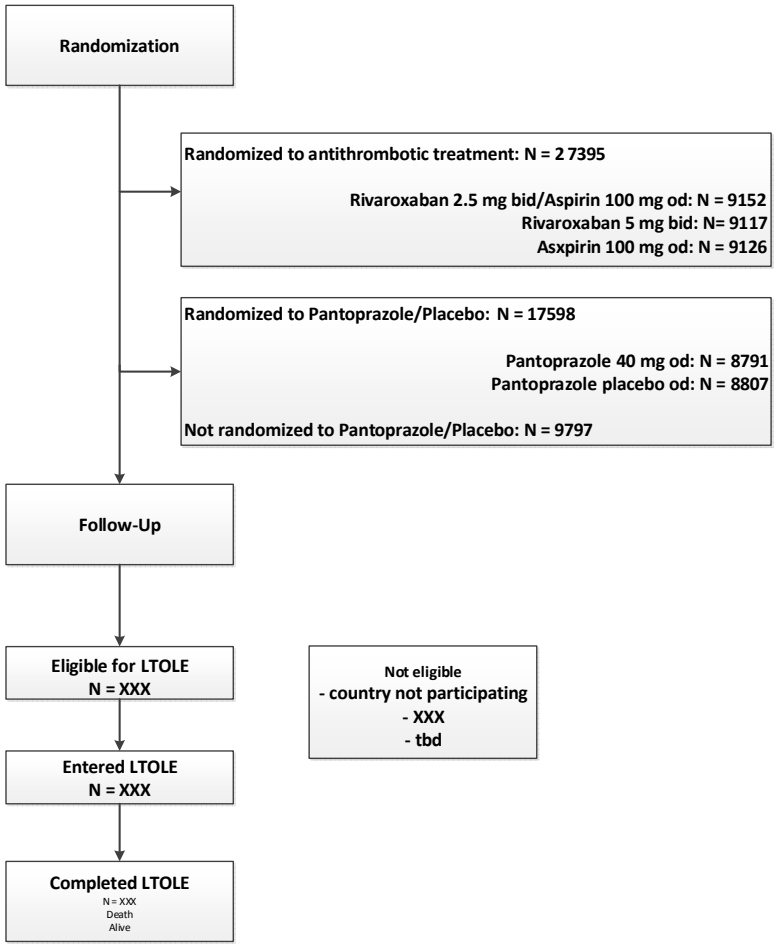
3. Study Design

For the general study design, please refer to integrated SAP, version 4.1.

LTOLE will provide open-label rivaroxaban 2.5 mg bid plus aspirin 100 mg od to COMPASS subjects until it is commercially available or for approximately 3 years from regulatory approval of LTOLE in a country, which ever comes first.

Not all sites who participated in COMPASS also participated in LTOLE. For subjects participating in COMPASS, the follow-up before LTOLE depends on the treatment group: follow-up for the antithrombotic portion ended in 2017 (release data of first clean database 04 AUG 2017), and follow up of pantoprazole/placebo randomization ended in 2018 (relase date of second clean data base 21 SEP 2018). First Patient First Visit for COMPASS LTOLE was achieved on 09 JAN 2018. Hence, patients who had not been randomized to pantoprazole/placebo have not been followed up during the time from close-out of the antithrombotic portion of the trial until they entered LTOLE. On the other hand, subjects randomized to pantoprazole/placebo may have had their final pantoprazole/placebo follow-up visit with or after LTOLE initiation visit. Hence, these subjects have been followed-up continuously.

LTOLE will involve an initiation visit and a follow-up period with follow-up visits every 6 months. The follow-up will be concluded with a final follow-up visit at the end of the study.



4. General Statistical Considerations

Please also refer to integrated SAP, version 4.1.

During LTOLE, no outcome events are planned to undergo an event adjudication process as was done during the initial part of the study and all events will be analyzed as reported by the investigators. Please refer to Section 6.1 for the arrangement of events during LTOLE and before LTOLE iniation.

4.1 Analysis Sets

The following analysis sets will be used for the analysis of the data after full close-out of the COMPASS trial after LTOLE.

- Intention-to-treat Analysis Set (ITT):
  The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, includes all subjects randomized to antithrombotic study treatment for the initial study part. The ITT set comprises both subjects randomized to pantoprazole/placebo and subjects not randomized to pantoprazole/placebo.

- Long-Term Open-Label Extension ITT Analysis Set (LTOLE ITT):
  The LTOLE ITT analysis set comprises all subjects who completed LTOLE initiaton visit (LTOLE initiation visit date entered).
- Long-Term Open-Label Extension Safety Analysis Set (LTOLE SAF):
  The LTOLE Safety analysis set will include all subjects who completed LTOLE initiaton visit and who received at least one dose of LTOLE medication.
  A subject is considered to have taken at least one dose of LTOLE study medication if date of permanent discontinuation of LTOLE study medication is later than the date of the completed LTOLE initiation visit.

4.2 Data scopes and censoring rules

The following data scopes will be considered:

- LTOLE follow-up
  - From date of LTOLE initiation visit to last LTOLE follow-up date
- LTOLE treatment emergent
  - From LTOLE initiation visit until last date of drug intake of LTOLE study medication + 2 days
- COMPASS follow-up
  - From randomization until last Follow-up date as defined in section 6.

5. Statistical Methodology

All data will be listed and all variables will be summarized by means of descriptive s tatistics according to their type.

Descriptive statistics such as mean, standard deviation, median, quartiles, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Event rates, life tables and Kaplan-Meier estimates will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data. Confidence intervals calculated similar to the main part of the study will be provided at a 2-sided level of 95% unless otherwise stated.

5.1 Population characteristics

The structure of the tables describing population characteristics will closely follow the tables provided for CDB1 but no statistical testing will be used to compare randomized treatment arms. Population characteristics will be displayed for the total of all subjects in LTOLE.

Baseline characteristics have not been collected for LTOLE initiation but at baseline of the COMPASS study. Hence, the data presented will represent the status at baseline of the COMPASS study, which may have been several years before LTOLE initiation.

5.1.1 Sample sizes

Study sample sizes will be tabulated overall for subjects in LTOLE as follows:

- Study sample sizes by region and country

• Study sample sizes by country and site

5.1.2 Subject disposition – Overview/Details at visits

Subject disposition will be presented with focus on the LTOLE related part of the study.

An overview of reasons not participating in COMPASS subjects approached to participateeparticipate in LTOLE will be given.

An overview of subjects entering LTOLE by randomized antithrombotic and pantoprazole treatment groups will be given. To help understand about the LTOLE entry, Kaplan-Meier estimates for the time from Final Rivaroxaban/Aspirin Follow-Up visit to LTOLE initiation visit will be provided.

A subject is considered as a LTOLE completer if the subject entered LTOLE and completed the LTOLE final vist or died.

A table presenting all subjects who changed study site will be presented including all cases of change of site during the study.

5.1.3 Visit and study drug adherence

The following will be tabulated :

- Number of subjects and reasons for premature permanent discontinuation of LTOLE study medication during LTOLE part
- Number of subjects and reasons for premature permanent discontinuation of LTOLE study follow up, i.e. consent withdrawn or lost to follow-up.

Kaplan-Meier estimates will be used to present

- time to the date of last dose of antithrombotic study treatment (calculated as days from LTOLE initiation visit), and,
- time to last follow-up date

all calculated as date of event – date of LTOLE initiation visit + 1.

Other details regarding visit adherence (e.g., visit completed in person, by telephone, through third party) and completion as well as study drug adherence collected via CRFs will be summarized using frequency tables by visit overall subjects in LTOLE.

In addition, after the final close-out of the study, a bulk batch listing including information of all bulk batches of the study will be provided.

5.1.4 Protocol Deviations

No per protocol analysis set will be defined. The number of subjects with major protocol deviations during LTOLE according to the CRF will be summarized overall. The types of deviations are described in the Data Management Plan.

5.1.5 Medical History

Medical history (recorded at initial randomization visit of the COMPASS study) will be evaluated by frequency tables for subjects in the LTOLE ITT analysis set and the LTOLE Safety analysis set, showing the number of subjects with medical history findings (i.e., listed conditions of previous diagnoses, diseases, or surgeries based on the CRF).

5.1.6 Demographics

Demographic data (with baseline defined as baseline of COMPASS study) will be evaluated descriptively for the LTOLE ITT analysis set and the LTOLE Safety analysis set for subjects on LTOLE rivaroxaban/aspirin.

Descriptive statistics (such as mean, standard deviation, median, quartiles, minimum and maximum) will be provided for continuous variables such as

- Age [years]
- Height [cm]
- Weight [kg]
- Waist and hip circumference [cm]
- Body mass index [kg/m²]

Counts and (appropriate) percentages will be provided for categorical variables such as

- Gender
- Ethnic group and ethnicity/race
- Tobacco use

5.1.7 Prior and Concomitant Medication

Frequency tables will be used to summarize the number of subjects with

- relevant antiplatelet agents and anticoagulant between Final Rivaroxaban/Aspirin Follow up visit and LTOLE initiation reported by the subject at the LTOLE initiation visit
- relevant concomitant medications at LTOLE initiation (non-study medications taken regularly for at least 1 month at the time of the LTOLE initiaion visit) and at final LTOLE follow up visit: non-study proton pump inhibitor, ACE inhibitor/ Angiotensin receptor blocker (ARB), alpha blocker or other vasodilator, diuretic, lipid lowering agent, calcium channel blocker, beta blocker, Non-steroidal anti-inflammatory drugs (NSAIDs), hypoglycemic agent, selective serotonin reuptake inhibitors (SSRIs).

5.2 Efficacy

LTOLE is designed as an open label single arm extension of the COMPASS study. No statistical testings are planned to compare treatment effects and efficacy results will be summarized descriptively with number of subjects with event, crude incidences, and incidence rates, where applicable.

5.2.1 Efficacy Variables for LTOLE

The outcome events from the following list will be analysed. For the arrangement of events in LTOLE and not in LTOLE, refer to section 6.1.

- The primary efficacy outcome (composite of myocardial infarction, stroke and cardiovascular death)

- Myocardial infarction
- Stroke
- Cardiovascular death
- Mortality (all-cause)
- Non-cardiovascular death
- Hospitalization
- Hospitalization for cardiovascular reasons

  The following reasons for admission will count as cardiovascular reasons:

  - Myocardial infarction
  - Stroke
  - Angina
  - Heart Failure
  - Venous thromboembolism
  - Revascularization
  - Amputation
  - Resuscitated cardiac arrest
  - Severe limp ischemia
  - Transient ischemuc attack
  - Stable agina pectoris
  - Cardiac arrhythmia
  - Syncope
  - Systemic artrial embolism
- Ischemic stroke
- Hemorrhagic stroke
- Uncertain stroke
- Severe limb ischemia
- Venous thromboembolism
- Pulmonary embolism
- Deep vein thrombosis
- Revascularization
- Vascular Amputation
- Angina (unstable, new or worsening)
- Heart failure

- Resuscitated cardiac arrest
- New cancer
- Recurrence of cancer
- GI event
- Overt bleeding of gastroduodenal origin
- Overt upper GI bleeding of unknown origin
- Bleeding of presumed occult GI origin
- Symptomatic gastroduodenal ulcer
- Upper GI Perforation
- Upper GI Obstruction
- Gastrointestinal Pain

5.2.2 Efficacy analysis for LTOLE

For the efficacy variables defined in section 5.2.1 in the LTOLE ITT analysis set in the LTOLE ITT data scope the number of subjects with event, crude incidences and incidence rates will be presented.

For all subjects of the ITT set in the COMPASS follow-up data scope, number of subjects with event and crude incidences will be presented. No incidence rates are planned to be presented in this data scope.

5.2.3 Subgroup Analyses

The efficacy analyses will be repeated for the following subgroups:

- Coronary artery disease (yes, no)
- Peripheral artery disease (yes, no)
- CAD and PAD (yes, no)
- CAD only, PAD only, CAD and PAD

5.3 Pharmacokinetics/Pharmacodynamics

Not applicable.

5.4 Safety

5.4.1 Safety Outcome Events for the Antithrombotic Randomization

Safety outcomes of the antithrombotic randomization will be reported with number and percentage of subjects for the LTOLE ITT analysis set as well as the LTOLE Safety analysis set. Incidence in events per 100-patient years will be presented.

For the LTOLE ITT analysis set

- during LTOLE follow-up

- and time from randomization up until LTOLE final follow-up. For this data scope no incidence rates will be presented.

For the LTOLE Safety analysis set, all events from LTOLE initiation up until last LTOLE study drug intake plus 2 days will be presented.

The following safety events will be tabularized:

- Modified ISTH major bleeding
    - Fatal
    - Critical organ bleeding (non-fatal)
    - Requiring re-operation (non-fatal and non- critical organ)
    - Hospitalization (non-fatal, non-critical organ, not leading to re-operation)
    - Gastrointestinal
    - Gastrointestinal (excl. oral cavity and esophagus)
    - Intracranial
- Minor bleeding

The bleeding classification will be assesed via an algorithm. The classification by the algorithm will be used as “adjudicated bleedings” and will be mainly used for safety analyses. In addition the bleedings as reported by inverstigators will be shown.

5.4.2 Other Events of interest

Other events of interest are:

- Pneumonia
- Clostridium difficile infection
- Other enteric infections
- Fracture
- Gastric atrophy
- Chronic kidney disease
- Diabetes
- Chronic obstructive lung disease
- Dementia

For these events the crude incidence of subjects in the LTOLE ITT analysis set having an event during LTOLE will be presented.

5.4.3 Adverse Events

Summaries of reported adverse events will be provided based on the LTOLE Safety analysis set using the LTOLE treatment emergent data scope as outlined in Section 4.2. The remaining principles of adverse event analyses will be applied as specified in the SAP, version 4.1.

5.4.4 Death

Deaths will be summarized by cardiovascular cause and non-cardiovascular cause

- from randomization to last trial contact (in ITT set)
- from LTOLE initiation to last trial contact (in LTOLE ITT set).

For these data scopes the number of subjects with an event, the crude incidences and the incidence rates will be presented.

5.4.5 COVID-19 related analyses

Subjects affected by the COVID-19 pandemic will be listed with the affected visits, the visit adherence and drug dispenstation method.

5.4.6 Pregnancies

Please refer to SAP, version 4.1.

5.4.7 Vital Signs

Not applicable.

5.4.8 Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation median, minimum and maximum) will be provided for the laboratory parameters serum creatinine and estimated glomerular filtration rate (eGFR) at the LTOLE initiation visit.

6. Definitions

Final LTOLE Follow-up Visit	Final visit at the end of the LTOLE follow-up of the COMPASS trial
Last LTOLE Follow-up Date	If consent was not withdrawn: <u>Last LTOLE Follow-up Date</u> = first of o date of death (if applicable) o maximum date of completed Final LTOLE Follow-up visit and last study drug intake, if Final LTOLE Follow-up Visit is completed o max (dates of visits completed during LTOLE, event dates during LTOLE). If consent was withdrawn: <u>Last LTOLE Follow-up Date</u> = first of • max (date of death, date of withdrawal, date of confirmed alive) o maximum date of completed Final LTOLE Follow-up visit (if applicable) and last study drug intake

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Last rivaroxaban/aspirin Follow-up Date	As defined for CDB1
Last pantoprazole/placebo Follow-up Date	As defined for CDB2
Last Follow-up Date	If subject is in LTOLE ITT set: Last Follow-up Date = Last LTOLE Follow-up Date Else If subject is in pantoprazole ITT set: Last Follow-up Date = Last pantoprazole/placebo Follow-up Date Else If subject is not randomized to pantoprazole/placebo: Last Follow-up Date = Last rivaroxaban/aspirin Follow-up Date

6.1 Arrangement of LTOLE and non-LTOLE events

In the LTOLE part of the study there is no adjudication of efficacy events, contrary to the antithrombotic as well the pantoprazole/placebo part of the study. For an arrangement for the whole study the following definitions hold:

- For event types not adjudicated at any time of the study: count all events as reported
- For events adjudicated at any time of the study:
  - Unrefuted events are all events confirmed in an adjudication plus the events that did not undergo adjudication
  - Investigator reported events are all events reported by the investigators regardless of any result of the adjudication process.

For the LTOLE part of the study the event CRF pages were simplified. The event “Bleeding leading to hospitalization” was not queried on the CRF page in the LTOLE event form. Thus all hospitalization with primary reason for admission “bleeding” will be counted for these events.

In the LTOLE event CRF the reasons for hospitalization are simplified and especially the other diagnoses is not divided into CV and non-CV reasons. Thus the event “Hospitalization for CV reasons” for the whole study is the combination of Hospitalizations for CV reasons as defined for CDB1 and CDB2 for the antithrombotic and pantoprazole/placebo part of the study and the events with reasons defined in section 5.2.1 as “cardiovascular reasons” for events during the LTOLE part of the study.

The event “Severe Limb Ischemia” was reported differently in the main part of the study and the LTOLE part. However, for the data scopes from randomization onwards the events of the antithrombotic and pantoprazole/placebo part will be combined with the events collected in LTOLE.

7. Document History and Changes in the Planned Statistical Analysis

Version 2 implements analyses with respect to COVID-19 pandemic, updated definition of Last LTOLE Follow-up date due to reported number of patients that reported to take study drug after final LTOLE visit and minor changes for the analyses of prior and concomitant medication.

8. References

CSR, Clinical Study Report of the COMPASS study, PH-39342, October 16, 2017.

SAP, version 4.1. Integrated Statistical Analysis Plan for the COMPASS study, March 31, 2017.

SAP; version 1.0. Integrated Statistical Analysis Plan for the COMPASS study for the PPI close-out, May 9, 2018.