

Document Type:	Study Protocol
Official Title:	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)
NCT Number:	NCT01776424
Document Date:	19 AUG 2015



Cover page of the integrated protocol

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)

This protocol version is an integration of the following documents / sections:

- Revised protocol, Version 1.1, dated 28 NOV 2012
- Amendment no. 6 (global) (described in Section 13.1) forming integrated protocol Version 2.0, dated 03 JUL 2014
- Amendment no. 8 (global) (described in Section 13.2) forming integrated protocol Version 3.0, dated 19 AUG 2015

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol. Local amendments were as filed in Japan (Amendments 1, 2, and 7), Sweden (Amendment 3), Germany (Amendment 4), and United Kingdom (Amendment 5).

**Title page - amended**

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)

Test drug: BAY 59-7939 / Rivaroxaban / Xarelto®

Study purpose: Comparative combination drug study for new indication

Clinical study phase: III Date: 19 AUG 2015

EudraCT no.: 2012-004180-43 Version no.: 3.0

Study no.: BAY 59-7939/15786

Coordinating center: PPD [REDACTED]

Sponsor: Bayer HealthCare AG, D-51368 Leverkusen, Germany

Coordinating center: PPD [REDACTED]

PPD [REDACTED] PPD [REDACTED]

Tel: PPD [REDACTED] Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915
United States
Tel: PPD [REDACTED]

The study will be conducted in compliance with the protocol, International Conference on Harmonization – Good Clinical Practice (ICH-GCP) and any applicable regulatory requirements.

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¹ PPD [REDACTED] changed as per Amendment 6. (See Section 13.1.2)



Signature of principal investigators

The signatories agree to the content of the final clinical study protocol as presented.

Name: PPD [Redacted]

Role: Co-principal investigator

Date: August 21, 2015

Signature: PPD [Redacted]

Name: PPD [Redacted]

Role: Co-principal investigator

Date: Aug 21/2015

PPD [Redacted]



Signature of site investigators

The signatories agree to the content of the final clinical study protocol as presented.

Name: _____ Role: Site investigator

Date: _____ Signature: _____

Name: _____ Role: Site investigator

Date: _____ Signature: _____

Signed copies of this signature page are stored in PPD _____ and the sponsor's study files and in the respective center's investigator site file.



Signature of the sponsor's medically responsible person – amended

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role: PPD

Date: 20 August 2015

Signature: PPD

² PPD changed as per Amendment 6. (See Section 13.1.2)



Synopsis - amended

Title	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)
Short title	Rivaroxaban for the prevention of major cardiovascular events in CAD or PAD (COMPASS)
Clinical study phase	III
Study objectives	<p>Primary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> • To determine whether rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (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 <p>Secondary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> • 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: (1) coronary heart disease death, myocardial infarction, ischemic stroke, acute limb ischemia; (2) cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia compared with aspirin 100 mg od in subjects with CAD or PAD³ • 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 in subjects with CAD or PAD <p>Objective for pantoprazole randomization</p> <ul style="list-style-type: none"> • To determine whether pantoprazole 40 mg od compared with placebo reduces the risk of upper gastrointestinal bleeding, ulceration, and gastrointestinal obstruction or perforation in subjects with CAD or PAD receiving antithrombotic medications

³ Text revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



Test drugs	Rivaroxaban, aspirin, and pantoprazole
Name of active ingredient	Rivaroxaban, aspirin, and pantoprazole
Dose(s)	<ul style="list-style-type: none"> • Rivaroxaban 2.5 mg, bid • Rivaroxaban 5.0 mg, bid • Aspirin 100 mg, od • Pantoprazole 40 mg, od
Route of administration	Per oral
Duration of treatment	Estimated average of 3-4 years
Reference drugs	Rivaroxaban placebo, aspirin placebo, and pantoprazole placebo
Name of active ingredient	Not applicable
Dose(s)	Not applicable
Route of administration	Per oral
Duration of treatment	Estimated average of 3-4 years
Indication	Coronary or peripheral artery disease
Diagnosis and main criteria for inclusion	<p>Subjects are eligible for inclusion if they:</p> <ul style="list-style-type: none"> • Meet criteria for CAD* and/or PAD⁴ <p>*Subjects with CAD must also meet at least one of the following criteria:</p> <ul style="list-style-type: none"> • Age ≥65 years, or • Age <65 years and documented atherosclerosis or revascularization involving at least 2 vascular beds[§], or at least 2 additional cardiovascular risk factors: <ol style="list-style-type: none"> 1) Current smoker (within 1 year of randomization) 2) Diabetes mellitus 3) Renal dysfunction with estimated glomerular filtration rate <60 ml/min 4) Heart failure 5) Non-lacunar ischemic stroke ≥1 month ago

⁴ Text added/deleted as per Amendment 6. (See Section 13.1.2)



	§ Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g. the aorta and arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, or kidneys.						
Study design	Randomized, double-blind, controlled trial with a 3 x 2 partial factorial design						
Methodology	<p>The study will comprise 4 periods: screening, run-in, follow-up, and washout.</p> <p>During the screening period, informed consent will be obtained and evaluations of subject eligibility will be performed. The run-in period will occur during the 28 days⁵ prior to initiation of study treatment, with the exception of subjects randomized Day 4-7⁵ after coronary artery bypass surgery who will not require a run-in. During run-in, subjects will discontinue any current anticoagulant therapy and will begin rivaroxaban placebo and 100 mg aspirin. Treatment of subjects who comply with the run-in treatment and who remain committed to the study, as well as those who are randomized Day 4-7⁵ after coronary artery bypass graft surgery will begin on Day 0, which will also signal the initiation of the follow-up period. Subjects will be randomized 1:1 to pantoprazole or pantoprazole placebo and then will be randomized 1:1:1 to rivaroxaban and aspirin or their matching placebos as shown in the treatment regimen design below:</p> <p>Randomized study treatments*</p> <table border="1"> <tbody> <tr> <td>Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od</td> <td>Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo</td> </tr> <tr> <td>Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole 40 mg od</td> <td>Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole placebo</td> </tr> <tr> <td>Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od</td> <td>Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo</td> </tr> </tbody> </table> <p>*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)</p> <p>Subjects will be followed for the duration of the study irrespective of whether they are receiving study treatment or whether they experience an outcome event. A final visit (Final Follow-up Visit) will mark the end of the follow-up period and will occur when a minimum of 2,200 subjects experience an event for the primary efficacy outcome. A final washout period visit (End of Washout Telephone Visit) will be conducted by telephone (performed 30 days after the Final Follow-up Visit).</p>	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo	Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole 40 mg od	Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole placebo	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo
Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo						
Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole 40 mg od	Rivaroxaban 5 mg bid + Aspirin placebo + Pantoprazole placebo						
Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo						
Type of control	For rivaroxaban: active control (aspirin). For pantoprazole: placebo						
Number of subjects⁵	Enrolled = approximately 29,940; randomized = approximately 27,400 in approximately 33 countries worldwide Approximately 29,940 subjects will be enrolled; approximately 28,300 will be						

⁵ Text modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



	<p>admitted to the run-in period and 2000 subjects will undergo coronary artery bypass graft but no run-in. A non-compliance rate of 10% is anticipated for those subjects in the run-in period; thus, approximately 27,400 subjects will be randomized (of which approximately 2000 subjects who underwent coronary artery bypass graft would be randomized without run-in) in approximately 33 countries worldwide.</p>
Primary variable	<p>The primary efficacy variable will be the time from randomization to the first occurrence of the primary efficacy outcome, the composite of myocardial infarction, stroke, or cardiovascular death.</p> <p>The primary safety variable will be the time from randomization to the first occurrence of the primary safety outcome, a modified International Society on Thrombosis and Haemostasis major bleeding.</p>
Plan for statistical analysis	<p>Analysis of the primary efficacy variable for rivaroxaban or aspirin randomization will be based on the intention-to-treat principle. Primary hypotheses will be tested using stratified log-rank tests. Relative risk reduction will be estimated with stratified Cox proportional hazards models.</p>



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List of abbreviations - amended

ACE	Angiotensin converting enzyme
AE	Adverse event
bid	Twice daily
BP	Blood pressure
bpm	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
cm	Centimeter
CRF	Case report form (either paper or electronic)
CT	Computed tomography
CV	Cardiovascular
dL	Deciliter
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DSS	Digit Symbol Substitution
DVT	Deep vein thrombosis
e.g.	<i>Exempli gratia</i> , for example
eGFR	Estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
EU	European Union
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
IB	Investigator's Brochure
ICH	International Conference on Harmonization
i.e.	<i>Id est</i> , that is
IEC	Independent ethics committee
in	Inch
INR	International normalized ratio
IRB	Institutional review board
IT	Information technology
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
ISTH	International Society on Thrombosis and Haemostasis
kg	Kilogram
lb	Pound
MD	Medical director/doctor
MI	Myocardial infarction



min	Minute
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
MoCA	Montreal Cognitive Assessment
MRU	Medical resource utilization
NL	National Leaders
NYHA	New York Heart Association
od	Once daily
PAD	Peripheral artery disease
PASS	Power Analysis and Sample Size software
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PPD	PPD
OR	Odds ratio
QA	Quality assurance
RRR	Relative risk reduction
SAE	Serious adverse event
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SUSAR	Serious unexpected suspected adverse reaction
USA	United States of America
US FDA	United States Food and Drug Administration
Xa	Activated coagulation factor X



1. Introduction

1.1 Background - amended

Globally an estimated 17.5 million people died from cardiovascular disease in 2005 (30% of all deaths) and this number is projected to increase to 20 million by 2015.(1)

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. Although CAD mortality rates have declined in high income countries over the past few years they have risen sharply in Asia, Latin America, the Middle East, and in India and China. Coronary heart disease remains responsible for about one-third of deaths in persons over the age of 35.(1,2)

Peripheral artery disease (PAD) of the lower extremities while often undiagnosed is a powerful risk marker of cardiovascular disease.(3) 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.(4) The disease prevalence is strongly age-related and like CAD the numbers of affected patients is rising because of the aging of the population. Best available estimates suggest that 27 million individuals in Europe and North America have PAD and it is likely that this number can be multiplied by at least 3- to 6-fold to estimate the global burden of disease.(5) 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 and 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 a 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.⁶

⁶ Text modified as per Amendment 6. (See Section 13.1.2)



Further information concerning the results of the rivaroxaban trials is provided in Section 1.2.1. Details concerning the pharmacology of rivaroxaban are provided in the investigator's brochure, located in the Manual of Operations.

The trial described herein, 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 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 usual care. In the (partial factorial) randomization, patients who do not have a continuous need for use of a proton pump inhibitor will be randomized to receive pantoprazole 40 mg od or placebo for the prevention of major upper gastrointestinal complications, and then randomized to receive rivaroxaban in combination with aspirin, rivaroxaban alone, or aspirin alone.⁷

1.2 Study rationale

1.2.1 Rivaroxaban - amended

Rivaroxaban has been tested in randomized controlled trials involving more than 80,000⁸ patients and has been used by millions of patients worldwide.

A pooled analysis of 4 trials comprising the RECORD program involving 12,729 patients undergoing hip or knee arthroplasty demonstrated that rivaroxaban given at a dose of 10 mg od compared with enoxaparin given at a dose of 30 mg bid or 40 mg od, significantly reduced the risk of symptomatic venous thromboembolism and mortality (odds ratio [OR] 0.48; 95% confidence interval [CI]: 0.30 to 0.76), without increasing the risk of major or clinically relevant non-major bleeding (OR 1.17; 95% CI: 0.93 to 1.46).⁽⁶⁾

The EINSTEIN venous thromboembolism treatment trials involving 9,447 patients with venous thromboembolism demonstrated that rivaroxaban 15 mg bid for 3 weeks followed by 20 mg od compared with initial low-molecular-weight heparin followed by warfarin (International Normalized Ratio [INR] 2.0 to 3.0) was associated with a similar or reduced risk of recurrent venous thromboembolism (deep venous thrombosis [DVT] trial, hazard ratio [HR] 0.68; 95% CI: 0.44 to 1.04; pulmonary embolism [PE] trial, HR 1.12; 95% CI: 0.75 to 1.68) with a similar or reduced rate of major bleeding during up to 12 months (DVT trial, HR 0.65; 95% CI: 0.33 to 1.30; PE trial, HR 0.49; 95% CI: 0.31 to 0.79).^(7,8) In the EINSTEIN extension study, rivaroxaban compared with placebo reduced the risk of recurrent venous thromboembolism by more than 80% (HR 0.18; 95% CI 0.09-0.39) at the expected cost of an increase in major bleeding (4 versus 0 events).⁽⁸⁾

The ROCKET AF trial involving 14,264 patients with atrial fibrillation at high risk of stroke demonstrated that rivaroxaban 20 mg od (15 mg od in patients with an estimated glomerular

⁷ Text modified as per Amendment 6. (See Section 13.1.2)

⁸ Text modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



filtration rate of 30 to 49 ml/min) compared with warfarin (INR 2.0 to 3.0) was non-inferior for the prevention of stroke or systemic embolism (HR 0.79; 95% CI: 0.66-0.96), with a significant reduction in life-threatening, intracranial, and fatal bleeding and a favorable effect on mortality.(9)

The ATLAS TIMI-51 study demonstrated that rivaroxaban 2.5 mg or 5 mg bid compared with placebo reduced the risk of myocardial infarction, stroke, or cardiovascular death by 16% (HR 0.84, 95% CI 0.74-0.96, p=0.008) in patients with a recent myocardial infarction, most of whom (92%) were also receiving dual antiplatelet therapy. The reduction in the primary efficacy outcome was driven by a reduction in both cardiovascular death and myocardial infarction, and rivaroxaban was also associated with 31% reduction in stent thrombosis (HR 0.69; 95% CI: 0.61-0.93). Rivaroxaban increased major and intracranial bleeding, but not fatal bleeding. (10) On a background of aspirin alone, rivaroxaban compared with placebo produced consistent benefits and appeared to be associated with no excess of major bleeding, although this was based on modest numbers of patients.

1.2.2 Aspirin and anticoagulants - amended

A large body of evidence from randomized controlled trials has established the efficacy of antithrombotic therapies for the prevention of cardiovascular events in high risk individuals.

Data from the Antithrombotic Trialists Collaboration meta-analysis demonstrate the efficacy of antiplatelet therapy for prevention of cardiovascular events.(11) Aspirin reduced the risk of myocardial infarction, stroke, or cardiovascular death by about one-quarter in patients with established coronary, cerebral, and PAD. A similar magnitude of benefit was evident across the different vascular beds.

Aspirin has also been demonstrated to be effective for the prevention of graft failure following coronary artery bypass graft (CABG) surgery.(11) Despite these results, however 1 in 3 patients undergoing CABG surgery with the placement of two or more graft have at least one blocked graft at 1 year of follow-up.(12) Graft failure is an independent predictor of myocardial infarction and death following CABG surgery.

The CAPRIE trial demonstrated that clopidogrel compared with aspirin reduced the risk of myocardial infarction, stroke, or cardiovascular death by additional 10% in patients with coronary, cerebral, or PAD.(13) Increasing the intensity of antiplatelet therapy by using the combination of aspirin and clopidogrel (dual antiplatelet therapy) compared with aspirin alone further reduced the risk of major cardiovascular events by 20% to 30% in patients with a recent acute coronary syndrome and in those undergoing percutaneous coronary intervention with stent insertion.(14) The replacement of clopidogrel by more potent P2Y₁₂ receptor antagonists such as prasugrel and ticagrelor has provided even greater benefit during the first 12 to 18 months after an acute coronary event.(15,16) However, a benefit of long term dual antiplatelet therapy (beyond the first 12-18 months) has not been demonstrated. The CHARISMA trial did not demonstrate a benefit of long-term aspirin and clopidogrel therapy (median 28 months) in patients with stable coronary, cerebral, or PAD or in those at high risk



of atherothrombotic vascular events, although a benefit was suggested in the subgroup of patients with symptomatic cardiovascular disease.(17)

Other studies have investigated the potential benefits of combined antiplatelet therapy for long-term prevention of cardiovascular disease. The TRA 2 P-TIMI 50 study demonstrated that the platelet protease-activated receptor 1 antagonist, vorapaxar added to standard therapy that included aspirin and clopidogrel, compared with standard therapy alone reduced the risk of myocardial infarction, stroke, or cardiovascular death by 13% at 3 years⁹ in patients with a history of myocardial infarction, ischemic stroke, or PAD, but at the cost of an increase in major and intracranial bleeding.(18) The PEGASUS trial demonstrated that 33 months of treatment with ticagrelor (90 mg twice-daily or 60 mg twice-daily) compared with placebo reduced the risk of cardiovascular death, myocardial infarction, or stroke by 15-16% (ticagrelor 90 mg: 7.85%, ticagrelor 60 mg: 7.77%, placebo 9.04%; p=0.008 and p=0.004, respectively) in patients with a history of myocardial infarction 1 to 3 years earlier. This came at the cost of a 2-3 fold increase in major bleeding (ticagrelor 90 mg: 2.60%, ticagrelor 60 mg: 2.30%, placebo 1.06%; p<0.01 for each dose vs. placebo), and there was no reduction in total mortality (ticagrelor 90 mg: 5.15%, ticagrelor 60 mg: 4.69%, placebo 5.16%; p=0.99 and p=0.14, respectively). (43)¹⁰

The DAPT trial randomized 9,961 patients with a history of coronary stenting with a drug eluting stent who had completed 12 months of dual antiplatelet therapy with a thienopyridine and aspirin to receive continuing clopidogrel 75 mg once daily or prasugrel 10 mg once daily or placebo for another 18 months. All patients continued receiving aspirin. Continuing treatment with a thienopyridine as compared with placebo reduced the rates of stent thrombosis by 71% (0.4% vs. 1.4%, p<0.001) and the composite, death, MI or stroke by 29% (4.3% vs. 5.9%, p<0.001) but at the cost of excess moderate or severe bleeding (2.5% vs. 1.6%, p=0.001) and a borderline significant 36% increase in all-cause death from any cause (2.0% vs. 1.5%, p=0.05). (44)¹¹

Excess mortality seen with extended dual antiplatelet therapy in the DAPT trial was confirmed in a subsequent meta-analysis of 10 randomized trials including 31,666 patients who had undergone coronary artery stenting comparing different durations of dual antiplatelet therapy. Shorter duration dual antiplatelet therapy was associated with an 18% reduction in all-cause mortality (HR 0.82, 95% CI 0.69-0.98; p=0.02), predominantly due lower non-cardiac mortality (HR 0.67, 0.51-0.89; p=0.006), with similar cardiac mortality (HR 0.93, 0.73-1.17; p=0.52). Shorter duration dual antiplatelet therapy was also associated with a lower risk of major bleeding (HR 0.58, 0.47-0.72; p<0.001), but a higher risk of myocardial infarction (HR 1.51, 1.28-1.77; p<0.001) and stent thrombosis (HR 2.04, 1.48-2.80; p<0.001).(45)¹¹

Anticoagulation with warfarin and the combination of warfarin and single agent antiplatelet therapy are also effective for the secondary prevention of cardiovascular events. A meta-analysis of randomized controlled trials involving more than 20,000 patients with CAD

⁹ Text modified as per Amendment 6. (See Section 13.1.2)

¹⁰ PEGASUS trial data added as per Amendment 8. (See Section 13.2.2)

¹¹ Paragraphs added as per Amendment 8. (See Section 13.2.2)



demonstrated that moderate intensity (INR 2.0 to 3.0) and high intensity (INR >2.8) warfarin compared with control reduced the risk of major cardiovascular events by 16% to 42%, establishing the efficacy of anticoagulant therapy for this indication.(19)

Direct randomized comparisons between anticoagulant and antiplatelet therapy have established the superior efficacy of warfarin for the prevention of major cardiovascular events in patients with established CAD but at the cost of increased bleeding. Thus, moderate intensity (INR 2.0 to 3.0) or moderate to high intensity (INR 2.5 to 3.5) warfarin compared with aspirin reduces the risk of myocardial infarction, stroke or cardiovascular death by 21% compared with aspirin (OR 0.79; 95% CI: 0.67 to 0.94), but this was at the cost of a more than 2-fold increase in major bleeding (OR 2.1; 95% CI 1.7 to 2.7).(19) A subsequent meta-analysis of randomized controlled trials involving 25,307 patients with established CAD demonstrated that the combination of warfarin (INR 2.0 to 3.0) and aspirin compared with aspirin alone reduced the risk of myocardial infarction, ischemic stroke, and all-cause mortality by 27% (OR 0.73; 95% CI: 0.63 to 0.84).(20) Once again the reduction in major cardiovascular events with warfarin-based therapy was accompanied by a more than 2-fold excess of major bleeding (OR 2.32; 95% CI: 1.63 to 3.29).

Warfarin has not been as extensively evaluated in patients with PAD but limited data suggest that it also offers benefits in this setting. The WAVE trial did not find a benefit of warfarin (INR 2.0 to 3.0) plus aspirin compared with aspirin alone for the prevention of myocardial infarction, stroke, or cardiovascular death in patients (n=2,161) with PAD (HR 0.92; 95% CI: 0.73-1.16).(21) However, the combination was associated with a more than 3-fold excess of life-threatening bleeding, and an exploratory post-hoc analysis excluding patients with major bleeding suggested an 18% relative risk reduction (HR 0.82; 95% CI: 0.62 to 1.05).

(PPD data on file)

Additional⁹ evidence for the efficacy and safety of oral factor Xa inhibitors for the prevention of major cardiovascular events comes from the recently completed AVERROES trial which demonstrated that the oral factor Xa inhibitor, apixaban, compared with aspirin not only reduced the risk of stroke but was also associated with numerically fewer myocardial infarctions with no significant increase in major bleeding.(22)

In summary, the randomized trials of antithrombotic therapy in patients with established atherothrombotic vascular disease have demonstrated the efficacy of single agent antiplatelet therapy (with aspirin or clopidogrel), anticoagulant therapy (warfarin), and the combination of single agent antiplatelet and anticoagulant therapy (aspirin and warfarin) for the long term secondary prevention of major cardiovascular events. Warfarin alone is substantially more effective than aspirin alone, and the combination of warfarin and aspirin provides even greater benefits, but is limited by excess of bleeding. Furthermore, because of the challenges of adjusting the dose of warfarin based on the results of routine laboratory monitoring, it is uncommonly used for long-term prevention of cardiovascular events.

The data summarized above support the hypothesis that when given in combination with, or instead of aspirin, a new anticoagulant such as rivaroxaban has the potential to yield



substantial benefits for the prevention of cardiovascular events in patients with established CAD or PAD.

1.2.3 Proposed rivaroxaban evaluation - amended

Based on the demonstrated efficacy and safety profile of rivaroxaban, rivaroxaban will be tested at a dose of 2.5 mg twice daily plus aspirin compared with aspirin alone, and at a dose of 5 mg twice daily compared with aspirin alone, in a 3-arm study. We hypothesize 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 potential¹² increase in bleeding. We also hypothesize that rivaroxaban compared with aspirin 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.

1.3 Benefit-risk assessment - amended

Considering the use of a new treatment for the prevention of cardiovascular disease, potential benefits need to be balanced against the risk. Bleeding is the most common complication of antithrombotic therapy and upper gastrointestinal bleeding accounts for the majority of bleeding complications. The risk of gastrointestinal bleeding increases with increasing intensity of antithrombotic therapy. When used for the prevention of cardiovascular disease, aspirin compared with placebo/no aspirin is associated with a 50 to 60% relative excess and a 0.5 to 1% absolute excess risk of major gastrointestinal bleeding.(23,24) In the ROCKET-AF trial, the 20 mg od dose was associated with an annualized rate of International Society on Thrombosis and Haemostasis (ISTH) major and non-major gastrointestinal (GI) combined bleeding rate of 3.2/100 patient years. (46)¹³

Major bleeding is an independent predictor of risk of death and other major cardiovascular events.(25,26) This excess risk may in part be explained by confounding, because patients who are more ill are more likely to experience adverse outcomes and are also more likely to bleed. However, even minor bleeding leads to discontinuation of effective antithrombotic therapies, thereby potentially compromising the efficacy of cardiovascular prevention and providing another possible explanation for the excess cardiovascular risk associated with bleeding. Effective strategies for the prevention of gastrointestinal bleeding have the potential to reduce morbidity and mortality directly caused by bleeding, but more importantly may also reduce ischemic cardiovascular events resulting from temporary or permanent interruption in patients treated with rivaroxaban.

Among patients taking aspirin or the combination of aspirin and clopidogrel, treatment with a proton pump inhibitor significantly reduces the risk of dyspepsia and peptic ulcer disease.(27) The United States Food and Drug Administration (US FDA) has issued a warning concerning

¹² Text added as per Amendment 6. (See Section 13.1.2)

¹³ The bleeding rate was updated as per Amendment 8 (was 2.23/100 patient years) and the reference was added.



the use of omeprazole but not pantoprazole in combination with clopidogrel. In the COMPASS trial, the efficacy of pantoprazole will be compared with placebo for the prevention of upper gastrointestinal bleeding, ulceration, obstruction or perforation in subjects randomized to the combination of rivaroxaban and aspirin, rivaroxaban alone, or aspirin alone, using a partial factorial design.

2. Study objectives - amended

Primary objectives 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, acute limb ischemia; cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia) compared with aspirin 100 mg od in subjects with CAD or PAD¹⁴
- 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 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 in subjects with CAD or PAD
- To collect medical resource utilization data to be incorporated in economic modeling for subjects with CAD or PAD

¹⁴ Text revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



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

Objectives for Day 4-7 post-CABG randomization¹⁵

- 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 od¹⁵
- 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 PAD¹⁵

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.¹⁶ COMPASS-MIND will be conducted concurrently with the main study in a subset of subjects at selected centers. A detailed description is included in Section 14.1.

3. Investigators and other study participants

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated and will be identified on the respective country-specific signature pages.

The COMPASS trial will be carried out in accordance with Good Clinical Practice (GCP) in close collaboration between Bayer and PPD

3.1 Study committees - amended

An Operations Committee will be responsible for ensuring that study execution and management of the study are of the highest quality. This committee is a subcommittee of the Steering Committee and will convene regularly to discuss and report on the ongoing supervision of the study. The committee will consist of the study chair and principal investigators, project leader, senior study coordinator, 2-3 sponsor representatives, and 3-4 National Leaders (NL).

A Steering Committee comprising members of the Operations Committee, university-based and sponsor-based scientists with clinical and methodological expertise, and NL from each

¹⁵ Text added as per Amendment 6. (See Section 13.1.2)

¹⁶ Sentence was revised as per Amendment 8. (See Section 13.2.2)



country, has overall responsibility for the study. The Steering Committee will be responsible for producing and conducting a scientifically sound study design and ensuring accurate reporting of the study. The Steering Committee will meet periodically to address and resolve scientific and practical issues encountered during the study.

An Events Committee consisting of members with clinical and methodological expertise will oversee the process of event adjudication. The process of event adjudication is detailed in the Event Adjudication Plan.¹⁷

An independent Data Safety Monitoring Board (DSMB) will be formed, comprising a chair, co-chair, and members who have recognized expertise in clinical trials, cardiovascular disease, and biostatistics, and who are not members of the Steering Committee or involved in the routine conduct of the COMPASS trial. The DSMB will be responsible for:

- monitoring efficacy and safety of the studied medications based on periodic updates throughout the study
- giving recommendations to the Steering Committee as to whether to continue, modify, or stop the study

The DSMB plays a key role in monitoring all aspects of the study. This committee will review aggregate data by treatment group in an unblinded fashion and thus are tasked with assessing risk and benefit for the study subjects.

At the first meeting of the DSMB, the DSMB charter and the frequency of meetings will be agreed upon. The DSMB will be supported at meetings by the designated PPD biostatistician (unblinded for the purpose of preparing reports for the DSMB). The study chair and/or the principal investigators will attend the open portion of the meeting to provide reports and respond to questions concerning the study.

3.2 Study coordination

The study will be coordinated by PPD, whose primary function is to facilitate and oversee the execution of the study in collaboration with the sponsor. PPD will keep the Operations and Steering Committees apprised of the progress and conduct of the study and will provide ongoing methodological and administrative support to the DSMB and will make available appropriate study data and/or documentation for these committees.

The NL are responsible for the conduct of the study within their respective countries. The NL are physicians with experience in both clinical management of cardiovascular disease and conduct of clinical studies in this field. Additional information is provided in the Manual of Operations.

¹⁷ The first 3 paragraphs of this section were revised as per Amendment 8. (See Section 13.2.2)



The Site Investigators are responsible for the conduct of the study within their respective centers. Additional information is provided in the Manual of Operations.

Whenever the term ‘investigator’ is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained, and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

3.3 Other study personnel and administrative functions

All other study personnel not included in Section 3 are identified in a separate personnel list as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center’s investigator site file.

A complete list of all participating centers and their investigators, as well as all required signature documents and other required documents, will be maintained in the trial master file.

4. Study design

4.1 Design overview - amended

This Phase 3, event-driven (at least 2,200 primary efficacy outcome events), randomized controlled trial will have a 3 x 2 partial factorial design and will randomize at least 27,400¹⁸ subjects who will receive treatment for an expected average duration of 3 to 4 years. The COMPASS trial will involve 4 periods: screening, run-in, follow-up, and washout.

Prescreening procedures may require informed consent in some countries. In all other study sites, informed consent will be obtained prior to the initiation of any screening procedures (Section 7.1.2.1).¹⁸ Screening will be performed to determine subject eligibility and will include the review of inclusion and exclusion criteria, physical measurements, laboratory evaluations, etc. (Section 7.1.2.2).¹⁹

The run-in period will occur during the 28¹⁹ 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 (Section 4.1.1). During run-in, subjects will discontinue any antithrombotic¹⁹ therapy and will begin study rivaroxaban placebo and study aspirin 100 mg.

¹⁸ Text modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

¹⁹ Text modified/added as per Amendment 6. (See Section 13.1.2)



Subjects who successfully complete the run-in period and 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 0, which will also signal the initiation of the follow-up period. Subjects without a continuous¹⁹ need for treatment with a proton pump inhibitor will be randomized 1:1 to the pantoprazole or pantoprazole placebo and all subjects (including those subjects who entered the study while already receiving a proton pump inhibitor) will then be randomized 1:1:1 to rivaroxaban alone, the combination of rivaroxaban and aspirin or aspirin alone, and their matching placebos as shown in [Table 4-1](#):

Table 4-1. Randomized study treatments*

Study Arm	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 of¹⁹ 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)

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 treatment adherence, treatment interruption, outcomes, and adverse events (AEs). Validated questionnaires (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]) will be administered at screening/run-in or randomization, or as soon as possible thereafter, as well as at Month 24 and at the Final Follow-Up visit to collect data on subject health and quality of life. The SAGE, MoCA, DSS, and EQ-5D will also be administered at the next study clinic visit after each outcome event. The Interheart Diet Questionnaire and the International Physical Activity Questionnaire will be administered at screening/run-in or randomization, or as soon as possible thereafter, and at Month 24. 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. The Final Follow-up Visit will occur as soon as possible after the required pre-specified number of subjects experience a primary efficacy outcome event for the antithrombotic randomization (close out is expected to occur over a period of about 3 months). A final washout period visit (End of Washout Telephone Visit) will be conducted by telephone (performed 30 days after the Final Follow-up Visit) to collect information on outcomes and protocol specific AEs. Adverse events will continue to be collected up to



30 days post study drug treatment. Bayer Global Pharmacovigilance will continue to follow the reported AEs until stabilized or resolved.²⁰

4.1.1 Subjects randomized after CABG surgery - amended

²¹Subjects randomized Day 4-7 after CABG surgery will undergo the same screening, follow-up, and washout as other COMPASS trial subjects but not run-in. Subjects are to sign informed consent before or after the surgery. Randomization will occur between Day 4-7 after surgery, at least 24 hours following the removal of chest tubes. The first dose of study drug should not be administered until at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis) (Section 7.1.1 Tabulated overview).

Subjects randomized Day 4-7 after CABG surgery will undergo computed tomography (CT) angiography at 1 year or later as part of the study protocol to assess graft patency unless they have a specific contraindication for CT angiography (e.g., contrast allergy, estimated glomerular filtration rate <30 ml/min). In the event the subject undergoes an invasive coronary angiography at approximately 1 year or later post CABG for any reason, a CT angiogram may not be required.

4.2 Primary efficacy and safety variables

The primary efficacy outcome for the rivaroxaban randomization is a composite of myocardial infarction, stroke, or cardiovascular death.

The primary safety outcome for the rivaroxaban randomization is a composite of:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring re-operation, and/or
- bleeding leading to hospitalization

4.3 Justification of the design

4.3.1 Overall design rationale - amended

The primary objective of the COMPASS trial is to determine whether rivaroxaban 2.5 mg bid + aspirin 100 mg od (Arm A) compared with aspirin 100 mg od (Arm C) reduces the risk of the composite of myocardial infarction, stroke, or cardiovascular death in subjects with CAD

²⁰ Paragraph revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

²¹ This section was revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



or PAD and, similarly, to determine whether rivaroxaban 5.0 mg bid + aspirin placebo od (Arm B) compared with aspirin 100 mg od (Arm C) reduces the risk of the composite of myocardial infarction, stroke, or cardiovascular death in subjects with CAD or PAD. The event-driven, double-blinded, 3 x 2 partial factorial design was selected for this study to support a rigorously controlled approach that would minimize study bias while focusing on the effects of treatment on the composite of the expected outcomes (myocardial infarction, stroke, or cardiovascular death) in this study population.

The benefit of increased²² intensity of antithrombotic therapy for the prevention of recurrent thrombotic cardiovascular events by adding a second agent to aspirin has been established in trials of dual antiplatelet therapy after an acute coronary syndrome when compared with aspirin alone. Additionally, a benefit has been shown in trials of combined warfarin and aspirin after myocardial infarction compared with aspirin alone.

The potential for the combination of rivaroxaban and aspirin to prevent thrombotic cardiovascular events after an acute coronary syndrome compared with aspirin alone has been investigated in previous rivaroxaban trials. A pooled post hoc analysis of the data from patients with an acute coronary syndrome in the Phase 2 and Phase 3 trials (ATLAS TIMI 46 and ATLAS TIMI 51) suggests that the effect size of rivaroxaban plus aspirin compared to aspirin alone for the composite outcome of CV death, myocardial infarction, and stroke (HR 0.66, 95% CI 0.46-0.96, p=0.026) (data on file) is at least double the effect size seen in the primary analysis of the ATLAS 51 trial (HR 0.84, 95% CI (0.74-0.96, p=0.008). For patients who do not have an ongoing indication for dual antiplatelet therapy but have a residual risk of cardiovascular events, it is expected that the addition of rivaroxaban 2.5 mg bid to standard dose of aspirin 100 mg will provide additional benefit compared to aspirin alone.

Not all trials of combined antithrombotic therapy have shown a benefit, but where there was a lack of benefit it could be explained either by the risk profile of the patients included in the trial (e.g., in the CHARISMA trial, clopidogrel plus aspirin was effective for secondary prevention in the subgroup of patients with established vascular disease but not in those without a history of symptomatic vascular disease) or by an excess of bleeding of the experimental treatment (e.g., in the WAVE trial, warfarin plus aspirin was associated with a substantial excess of bleeding compared with aspirin which substantially attenuated the benefits).

To date, no trials have directly compared a new anticoagulant with aspirin for long-term secondary prevention of cardiovascular disease. Prior efforts to identify more effective antithrombotic treatments than aspirin have focused on new antiplatelet therapies (terutroban, a platelet thromboxane receptor antagonist; clopidogrel, prasugrel, and ticagrelor, P2Y₁₂²² antagonists; and vorapaxar, a PAR-1 receptor antagonist) and warfarin. In most cases, the benefit of the experimental treatment has either been of insufficient magnitude to warrant a switch in treatment (e.g., clopidogrel, prasugrel) or has been accompanied by a substantial excess of bleeding (e.g., vorapaxar, ticagrelor²³, warfarin). The promise of a new

²² Text modified as per Amendment 6. (See Section 13.1.2)

²³ “ticagrelor” added as per Amendment 8 based upon the recently published PEGASUS trial.



anticoagulant such as rivaroxaban (rivaroxaban 5.0 mg as explored in Arm B) is highlighted by the results of the AVERROES study which demonstrated superior efficacy of apixaban compared with aspirin for stroke prevention in patients with atrial fibrillation as well as numerically fewer myocardial infarctions and no significant excess in bleeding.⁽²²⁾

The use of aspirin-alone antiplatelet therapy for atherosclerotic CAD and PAD is widely accepted.²⁴ As such, most patients will be candidates for aspirin monotherapy. This is in line with current practice guidelines and the current prescribing information for secondary prevention. The dose of aspirin being tested in COMPASS is 100 mg/d.

4.4 Final follow-up visit and end of study

The primary analysis will be based on the events that occur between randomization and 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 visit will occur when at least 2,200 subjects experience an event for the primary efficacy outcome. 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. The Final Follow-up Visit and the subsequent 30-day washout period will occur nearly simultaneously (as scheduling permits) for all study subjects.

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the telephone call at the end of the 30 day washout period for the last subject for all centers in the respective country has occurred. The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

5. Study population - amended

Multiple strategies will be employed to identify subjects potentially eligible for this study. These will include (but are not restricted to) database screening, chart screening, and patient screening at physician offices and at internal medicine, cardiology, and vascular disease/imaging clinics. The approach at individual centers will vary according to physician, office, or hospital environment, and ethical considerations.

Approximately 28,300 eligible subjects will be admitted to the run-in period and an additional 2000 will be enrolled post CABG and without run-in. Approximately 10% of run-in subjects are expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study will randomize approximately 27,400 men and women with objectively confirmed CAD or PAD from approximately 33 countries worldwide.²⁵

Subjects with high risk of incident cardiovascular disease will be enrolled in the study. Subjects will be treated with rivaroxaban, the combination of rivaroxaban and aspirin, or

²⁴ Sentence revised as per Amendment 8. (See Section 13.2.2.)

²⁵ Text modified/added as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2.)



aspirin on top of usual care. Investigators in the study are selected based on their qualifications and ability to enroll and treat these subjects in accordance with the protocol and applicable standard of care.²⁶

For the purpose of determining eligibility for this trial, subjects meeting criteria for CAD must have one or more of the following:²⁶

- Myocardial infarction within the last 20 years²⁶, or
- Multi-vessel coronary disease* with symptoms or history of stable or unstable angina, or²⁶
- Multi-vessel percutaneous coronary intervention (PCI), or
- Multi-vessel CABG surgery

*Refers to stenosis of greater than or equal to 50% in 2 or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g. exercise or pharmacologic) suggestive of significant ischemia in 2 or more coronary territories; or in 1 coronary territory if at least one other territory has been revascularized²⁶

For the purpose of determining eligibility for this trial, subjects meeting criteria for PAD must have one or more of the following:²⁶

- Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization²⁶ of the iliac, or infrainguinal arteries, or
- Previous limb or foot amputation for arterial vascular disease (i.e., excludes trauma), or
- History of intermittent claudication and one or more of the following: 1) ²⁶ an ankle/arm blood pressure (BP) ratio < 0.90, or 2) ²⁶ significant peripheral artery stenosis ($\geq 50\%$)²⁶ documented by angiography, or by duplex ultrasound, or
- Previous carotid revascularization (e.g., endarterectomy, stenting) or²⁶ asymptomatic (i.e., no ipsilateral stroke or transient ischemic attack within 6 months) carotid artery stenosis $\geq 50\%$ ²⁶ as diagnosed by duplex ultrasound or angiography.

5.1 Eligibility

In order to be eligible for study entry, potential subjects must meet all of the inclusion criteria and none of the exclusion criteria listed below.

²⁶ Text modified as per Amendment 6. (See Section 13.1.2)



5.1.1 Inclusion criteria - amended

- Willing and able to provide written informed consent
- Meet criteria for CAD* and/²⁷or PAD

*Subjects with CAD must also meet at least one of the following criteria²⁷:

- Age ≥ 65 , or
- Age < 65 and documented atherosclerosis or revascularization involving at least 2 vascular beds^{§, 27} or at least 2 additional risk factors:
 - 1) Current smoker (within 1 year of randomization)²⁷
 - 2) Diabetes mellitus
 - 3) Renal dysfunction with estimated glomerular filtration rate < 60 ml/min
 - 4) Heart failure
 - 5) Non-lacunar ischemic stroke ≥ 1 month ago

§ Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g. the aorta and arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, or kidneys.²⁷

5.1.2 Exclusion criteria - amended

- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known ejection fraction $< 30\%$ or New York Heart Association (NYHA) class III or IV symptoms
- Estimated glomerular filtration rate (eGFR) < 15 mL/min
- Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
- Known non-cardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer) or that increases the risk of an adverse reaction to study interventions.
- History of hypersensitivity or known contraindication for rivaroxaban, aspirin, pantoprazole, or excipients, if applicable.²⁷

²⁷ Text modified/added as per Amendment 6. (See Section 13.1.2)



- Systemic treatment with strong inhibitors of both CYP 3A4 and p-glycoprotein (P-gp) (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine²⁸
- Any known hepatic disease associated with coagulopathy
- Subjects who are pregnant, breastfeeding, or are of childbearing potential, and²⁸ sexually active and not practicing an effective method of birth control (e.g. surgically sterile²⁸, prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization)
- Previous assignment to treatment during this study
- Concomitant participation in another study with investigational drug²⁸
- Known contraindication to any study related procedures²⁸

An additional exclusion for the pantoprazole randomization is:

- Need for continuous²⁸ treatment with a proton pump inhibitor

5.2 Discontinuation of subjects from study treatment - amended

All subjects will be encouraged to remain on treatment and under observation for the full duration of the study. However, at any time during the study and without giving reasons, subjects may withdraw from the study at their own request or at the request of their legally acceptable representative. The subject will not suffer any disadvantage as a result. In all cases, the reason for permanent discontinuation of study treatments (including “at the subject’s request”) must be recorded in the case report form (CRF) and in the subject's medical records.

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. Withdrawal of this consent must be made separately. 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.²⁹ Additionally, survival status and outcome information must be determined for all subjects.²⁸**

²⁸ Text modified as per Amendment 6. (See Section 13.1.2)

²⁹ Sentence revised as per Amendment 8. (See Section 13.2.2)



5.2.1 Replacement

No subject replacements are permitted in this study.

5.3 Subject identification

Each subject will receive a unique identification number, which will represent both the assigned study center number and subject number. The center number will be pre-assigned by PPD. The subject identification number, consisting of center number and subject number must be entered in the PPD randomization and drug management system to obtain the assignment of study treatment. Once assigned to a subject, the subject identification number will not be re-used.

6. Treatments

6.1 Treatments to be administered - amended

The study drugs to be administered in this trial include the antithrombotic drugs, rivaroxaban and enteric-coated³⁰ aspirin; the proton pump inhibitor pantoprazole; and their matching placebos.

6.1.1 Run-in - amended

During the run-in period, Day -28³⁰ to Day -1³¹, eligible subjects (excluding those who are randomized³¹ Day 4-7³⁰ after CABG surgery) who have signed informed consent and stopped non-study anticoagulants and aspirin will receive rivaroxaban placebo bid and aspirin 100 mg od. Study pantoprazole or pantoprazole placebo will not be administered during the run-in period.

All doses will be provided in tablet form for oral administration.

6.1.2 Randomization - amended

Subjects who have completed the run-in period with adherence to treatment with rivaroxaban placebo bid and aspirin 100 mg od of at least 80% except for extenuating circumstances,³⁰ and who wish to continue in the study will be randomized. Subjects being randomized after run-in³⁰ and those who are being randomized Day 4-7³⁰ after CABG surgery (Section 7.1.1 Tabulated overview) and who do not have a continuous³⁰ need to take a proton pump inhibitor, will initially be randomized 1:1 to receive pantoprazole 40 mg od or matching placebo od, stratified by center. All subjects will then be randomized 1:1:1 to anticoagulant therapy stratified by center and by proton pump inhibitor use (randomized to pantoprazole,

³⁰ Text modified/added as per Amendment 6. (See Section 13.1.2)

³¹ Text deleted as per Amendment 6. (See Section 13.1.2)



randomized to pantoprazole placebo, not randomized because subject is already taking a proton pump inhibitor) as shown below:

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

Arm B: rivaroxaban 5.0 mg bid + aspirin placebo od

Arm C: rivaroxaban placebo bid + aspirin 100 mg od

All doses will be provided in tablet form for oral administration.

Follow-up will continue until a minimum of 2,200 subjects experience an event for the primary efficacy outcome for the rivaroxaban randomization. These events are expected to accumulate over approximately 4-5 trial years after randomization of the first subject.

6.2 Identity of study treatment - amended

All study drugs will be labeled in the local language according to the requirements of local law and legislation and will include no information about the subject except for the medication number. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request. For the purpose of this study, the term "aspirin" is used interchangeably with the term "acetyl salicylic acid".³²

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

6.3 Treatment assignment - amended

For subjects who successfully complete the run-in period, the investigator or delegate will access the PPD randomization and drug management system to confirm eligibility and compliance to run-in rivaroxaban placebo bid and aspirin od and to obtain the randomized treatment allocation.³³

The PPD randomization and drug management system will assign the subject a unique number for each medication that corresponds to one of the treatments listed in [Table 4-1](#).

³² Text added as per Amendment 6. (See Section [13.1.2](#))

³³ Sentence revised as per Amendment 8. (See Section [13.2.2](#))



6.4 Dosage and administration - amended

Study medication will be taken orally. Study rivaroxaban/rivaroxaban placebo is taken twice daily (generally morning and evening, approximately 12 hours apart) and study aspirin/aspirin placebo and study pantoprazole/pantoprazole placebo are taken once daily, generally in the morning. The first doses of study drug should be administered on the day of randomization, or at least 12 hours after the last dose of antithrombotic medication if being randomized post-CABG.³⁴

If a dose of study rivaroxaban/rivaroxaban placebo is missed and less than 6 hours have elapsed since the time that the missed dose was due, it should be taken immediately. If more than 6 hours have elapsed since the missed dose was due, the dose should be skipped and the next dose of study rivaroxaban should be taken according to schedule.

If a dose of study aspirin/aspirin placebo or study pantoprazole/pantoprazole placebo is missed it should be taken as soon as the subject becomes aware that the dose has been missed.

6.4.1 Dose modifications - amended

The investigator should interrupt study drug for a given subject if continuation is deemed to be detrimental to the subject's well-being. All subjects who interrupt study drug should resume treatment when possible. If there is concern that the subject may be intolerant of study treatments or if the subject is reluctant to take the full dose of study treatments, a possible approach to restarting study medications is to reduce the frequency of dosing (eg, to once-daily or alternate-daily).³⁵ Irrespective of whether or not treatment is resumed, all subjects must be followed according to the study protocol until the end of the study.

Permanent study drug interruption should be recorded on the corresponding follow-up case report form, giving the date and primary reason for stopping the study drug. If one of the study treatments needs to be discontinued³⁶, other study treatments must be continued. For example, if study rivaroxaban/rivaroxaban placebo is interrupted, study aspirin/aspirin placebo and study pantoprazole/pantoprazole placebo should be continued.

6.4.2 Dose modifications and treatment guidance - amended

This section provides a general guide for investigators on the management of subjects who develop intercurrent illnesses or bleeding during the course of the COMPASS trial. The guidance provided in this section does not replace clinical judgment nor usual care³⁶ in determining the appropriate management strategy for individual subjects. For specific treatment guidance with study pantoprazole/pantoprazole placebo see Section 6.9.4³⁶

³⁴ Sentence revised as per Amendment 8. (See Section 13.2.2)

³⁵ Sentence revised as per Amendment 8. (See Section 13.2.2)

³⁶ Text modified/added as per Amendment 6. (See Section 13.1.2)



6.4.2.1 Guidance for the treatment of subjects who require an invasive procedure - amended

If the subject requires an invasive procedure that is associated with a standard or high risk of bleeding (i.e., any procedure that is not considered “minor”), study rivaroxaban/rivaroxaban placebo must be interrupted. Study aspirin/aspirin placebo may also be interrupted, at the discretion of the investigator. If study aspirin/aspirin placebo is interrupted, non-study aspirin may be used.³⁷

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, rivaroxaban/rivaroxaban placebo should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Rivaroxaban/rivaroxaban placebo should be restarted after the invasive procedure or surgical intervention as soon as possible, provided the clinical situation allows and adequate hemostasis has been established.

If surgery is urgent or needed in an emergency situation, the risk of bleeding must be weighed against the risk of delaying surgery. The total daily dose of rivaroxaban in subjects randomized to receive 5 mg bid is equivalent to the prophylactic dose that was tested in major orthopedic surgery trials and this dose of rivaroxaban is not expected to substantially increase the risk of bleeding. The total daily dose of rivaroxaban in subjects randomized to receive rivaroxaban 2.5 mg bid is only half that of the orthopedic thromboprophylaxis dose although these subjects will also be receiving treatment with aspirin. If there is a concern about the risk of bleeding in a subject who requires urgent or emergency surgery, unblinding may be considered but should *only* be performed if knowledge of randomized treatment allocation will influence clinical management (Section 6.5). A two-unit single donor platelet transfusion in subjects treated with the combination of aspirin and rivaroxaban may restore the capacity to generate thromboxane and thereby overcome the antiplatelet effects of aspirin.⁽²⁹⁾

6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery - amended

CABG surgery can occur immediately prior to randomization or it may occur in randomized subjects who later develop a need for the surgery.

Subjects who are scheduled to be randomized Day 4-7 after CABG surgery will not participate in the run-in phase (Section 4.1.1). Randomization should only be performed between Day 4-7 post-CABG and at least 24 hours following the removal of chest tubes. Study drug should not be administered until at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis).³⁸

³⁷ Text deleted as per Amendment 6. (See Section 13.1.2)

³⁸ Text modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



Subjects who are scheduled for CABG surgery during the course of the trial ideally should interrupt study rivaroxaban/rivaroxaban placebo at least 24 hours before CABG surgery in order to minimize the risk of bleeding. Study aspirin/aspirin placebo may be interrupted and/or non-study aspirin may be used or at the discretion of the investigator. The timing of resumption of study antithrombotic therapy after surgery is at the discretion of the investigator but, in general, study rivaroxaban/rivaroxaban placebo or study aspirin/aspirin placebo should be resumed once the chest tubes are removed and hemostasis is secure. Study rivaroxaban/rivaroxaban placebo should be interrupted if subjects require in-hospital anticoagulant thromboprophylaxis. In all cases, the goal should be to resume study antithrombotic drugs within 14⁴⁰ days and prior to being discharged from hospital.³⁹

6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting - amended

Study rivaroxaban/rivaroxaban placebo should be interrupted in subjects who require anticoagulant or dual antiplatelet therapy because of an acute coronary syndrome or need for percutaneous coronary intervention with stenting. Standard antiplatelet therapy, including loading doses of aspirin and clopidogrel (or prasugrel or ticagrelor) can be administered according to usual practice. Study aspirin/aspirin placebo may be continued. Standard anticoagulant therapy can be used without regard to the timing of the most recent dose of study rivaroxaban/rivaroxaban placebo because the doses of rivaroxaban being tested in the COMPASS trial are lower than the 15⁴⁰ or 20 mg dose given for stroke prevention in atrial fibrillation and the half-life is short, 5-13 hours.

Subjects who remain on long term dual antiplatelet therapy may commence “interim study rivaroxaban/rivaroxaban placebo” once any non-study anticoagulant therapy is stopped. Study aspirin/placebo may be continued.⁴¹ The difference between interim study rivaroxaban/rivaroxaban placebo and study rivaroxaban/rivaroxaban placebo is that during the period of dual antiplatelet therapy all subjects will receive rivaroxaban at a dose of 2.5 mg bid (i.e., the dose of rivaroxaban in those previously allocated 5 mg bid will be reduced to 2.5 mg bid). Subjects previously allocated 2.5 mg bid will continue on the same dose whereas those previously allocated rivaroxaban placebo will remain on placebo. Interim study rivaroxaban will be allocated via the PPD randomization and drug management system. All subjects should resume originally allocated study rivaroxaban/rivaroxaban placebo once non-study dual antiplatelet therapy is stopped and they are not being treated with non-study anticoagulants. When switching back to originally allocated study anticoagulant, interim study anticoagulant therapy should be stopped.³⁹

³⁹ Text deleted as per Amendment 6. (See Section 13.1.2)

⁴⁰ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁴¹ The first sentence was revised and the second sentence was added as per Amendment 8. (See Section 13.2.2)



6.4.2.4 Guidance for the treatment of subjects who overdose on study rivaroxaban/rivaroxaban placebo – amended

If rivaroxaban overdose is suspected, the use of activated charcoal up to 8 hours after overdose to reduce absorption may be considered. Due to its low solubility, rivaroxaban absorption plateaus at doses of 50 mg and above, thus limiting exposure in the majority of subjects. Gastrointestinal absorption of rivaroxaban is reduced in subjects exposed to high oral doses and thus the anticoagulant effect of an overdose of rivaroxaban is expected to be limited. If available, consideration may be given to the use of a specific reversal agent.⁴²

6.4.2.5 Guidance for the treatment of subjects who experience a major bleed - amended

Temporary discontinuation of rivaroxaban is expected to be sufficient to control bleeding in most cases because the drug half-life is only 5-13 hours. Local measures should be applied if needed to control bleeding (e.g., local pressure, endoscopy and injection of a bleeding vessel, embolization) and intravenous fluids and blood transfusion support should be provided as indicated. In the rare case of life-threatening bleeding, the investigator may consider obtaining advice from a hematologist. Animal studies suggest that both prothrombin complex concentrates and recombinant factor VIIa partially restore hemostasis following treatment with factor Xa inhibitors such as rivaroxaban and a randomized trial involving healthy subjects treated with rivaroxaban has demonstrated that prothrombin concentrates reverse prolongation of the prothrombin time.⁽³⁰⁾ Rivaroxaban cannot be dialyzed as it is highly protein bound. If available, consideration may be given to the use of a specific reversal agent.⁴³

6.4.2.6 Guidance for the treatment of subjects who develop a stroke and who are being considered for reperfusion therapy - amended

The decision to use reperfusion therapies (including intravenous, intra-arterial thrombolysis, or mechanical endovascular approaches) in acute ischemic stroke should follow local practice, experience, and guidelines. At present there are limited data to guide treatment in this setting in subjects taking rivaroxaban. The following guidance is intended to aid clinical decision making in this setting.

At or around the time of the peak drug levels (we suggest in the first 6 hours after a dose), clinicians may choose to unblind and to avoid thrombolysis if the subject is taking rivaroxaban. Alternatively, if it is possible to obtain a rivaroxaban anti-Xa level in this time period, clinicians may use this information to decide on the appropriateness of starting thrombolysis. Endovascular therapy with clot extraction can proceed whether or not the subject is receiving rivaroxaban without the need to unblind.⁴⁴

⁴² This paragraph was revised as per Amendment 8. (See Section 13.2.2)

⁴³ This paragraph was revised as per Amendment 8. (See Section 13.2.2)

⁴⁴ Section was added with Amendment 8. (See Section 13.2.2)



6.5 Blinding

Subjects, site personnel, sponsor personnel, PPD staff (with the exceptions mentioned below), persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock. Randomization data are to be kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: (1) PPD information technology (IT) computer programmers who work on the PPD randomization and drug management system; and (2) the PPD unblinded biostatistician who prepares reports for the DSMB and provides unblinded information to Bayer for required regulatory reporting (suspected unexpected serious adverse reactions [SUSAR] reporting). These individuals will not be involved in the day-to-day running of the study.

In compliance with applicable regulations, in the event of a SUSAR that was believed to be related to study treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators.

Emergency unblinding by the investigator

Emergency unblinding should only be undertaken when it is essential for subject safety and will only be provided for the treatment that requires unblinding. Most often, study drug interruption and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Detailed information concerning unblinding procedures is provided in the Manual of Operations. In case of unblinding, only those individuals who are required to know treatment allocation may be given this information. All others must remain blinded to treatment, including the subject. All subjects should resume study treatments after recovery if it is medically appropriate to do so and should be followed until the end of the study.

6.6 Drug logistics and accountability - amended

Each study site will be supplied with study medication kits for the run-in (2 pill bottles) and additional study supply for the follow-up phase (and will be re-supplied throughout the study, as needed). The study medication supply will have appropriately labeled packaging according to national law and GMP ruling. The study medication packaging has a 2-part tear-off label. A unique medication number will be printed on each part of this label, which corresponds to one of the unique treatment arms for the blinded randomized treatment period. Investigator staff will identify the study drug package(s) to dispense to the subject by accessing the PPD randomization and drug management system and obtaining the medication number(s). At the time of dispensing, one part of the 2-part label will be removed and affixed to the subject's drug dispensing log and the other will remain on the study medication package.

All study drugs will be stored at the investigational site in accordance with GCP and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry



dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm the date⁴⁵ of receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the agreed and specified procedures. Specific instructions for the study drug recordkeeping are provided in the Study Operations Manual.

Written instructions on medication destruction will be made available to affected parties as applicable.

6.7 Treatment compliance

The investigator should promote compliance by counseling the subject to take the study drug as prescribed. The subject should be instructed to contact the investigator if unable for any reason to take the study drug as prescribed.

Treatment compliance will be assessed by confirmatory pill counts to be conducted at each study visit.

6.8 Post-study therapy - amended

At the conclusion of treatment with study medication, the study staff should encourage the subject to resume treatment with open-label aspirin as indicated.⁴⁶

6.9 Prior and concomitant therapy - amended

As described in Section 5.1.2, Exclusion criteria, the use of the following agents is not permitted at study entry: systemic treatment with strong inducers of CYP 3A4 (e.g. rifampicin) and inhibitors of both⁴⁷ CYP 3A4 and P-gp (e.g., systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir) (see Section 6.9.1)⁴⁸. Additionally, subjects with a need for dual antiplatelet therapy or oral anticoagulant therapy are not eligible for inclusion in COMPASS.

During the study, all randomized subjects should continue to receive any ongoing medications, with the exception of the subject's own aspirin, which must be discontinued at the time of commencing the run-in, and treatments that are contraindicated in combination with rivaroxaban. Subjects may receive all medications that their treating physicians believe are necessary. If subjects develop a need for treatments that may interfere with the efficacy or safety of study drugs or for treatments that are taken in place of study drug, they must temporarily discontinue the relevant study drug (study rivaroxaban/rivaroxaban placebo,

⁴⁵ Text deleted as per Amendment 6. (See Section 13.1.2)

⁴⁶ Text revised as per Amendment 8. (See Section 13.2.2)

⁴⁷ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁴⁸ The cross-reference to Section 6.9.1 was added as per Amendment 8.



aspirin/aspirin placebo, or pantoprazole/pantoprazole placebo) until such time that the interacting treatment is discontinued. Study aspirin/aspirin placebo may be continued⁴⁹ irrespective of the need for aspirin or dual antiplatelet therapy.

6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors and CYP 3A4 inducers - amended

Strong inhibitors of both CYP 3A4 and p-glycoprotein increase plasma concentrations of rivaroxaban and are contraindicated in subjects taking rivaroxaban. These include systemic azole antifungal drugs (e.g. ketoconazole, itraconazole, posaconazole, etc.), and HIV protease inhibitors. Additionally, strong inducers of CYP 3A4 such as rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine can reduce the plasma concentrations of rivaroxaban. If any of these treatments are needed, randomized study rivaroxaban/rivaroxaban placebo must be temporarily discontinued and open-label aspirin should be begun.⁵⁰

6.9.2 Clopidogrel (or any other non-study antiplatelet treatment) - amended

Subjects who develop a need for treatment with non-study dual antiplatelet therapy, such as aspirin plus clopidogrel (e.g., subjects who experience an acute coronary syndrome, those who undergo percutaneous coronary intervention with stent insertion) must interrupt⁴⁷ study treatment of⁴⁷ rivaroxaban/rivaroxaban placebo. Study rivaroxaban/rivaroxaban placebo must be restarted once dual antiplatelet therapy is stopped (i.e., after completion of an adequate duration of dual antiplatelet treatment). Additional guidance is provided in Section 6.4.2.3.

6.9.3 Anticoagulant treatment - amended

Subjects who develop a need for anticoagulant therapy (e.g., thromboprophylaxis in subjects undergoing major orthopedic surgery, acute venous thromboembolism, atrial fibrillation, mechanical aortic valve replacement) must interrupt study rivaroxaban/rivaroxaban placebo. Study rivaroxaban/rivaroxaban placebo must be restarted in subjects who no longer have a need for non-study anticoagulant therapy (e.g., after completion of anticoagulant thromboprophylaxis or anticoagulant treatment for venous thromboembolism). In subjects who develop a need for anticoagulant therapy, study aspirin/aspirin placebo may also be interrupted, at the discretion of the investigator.⁵¹

If prophylactic anticoagulation is required, subjects should start the first dose of open prophylactic anticoagulation at the time that the next dose of study rivaroxaban/rivaroxaban placebo is due. If study drug is interrupted and the subject is transitioned to an anticoagulant with a slow onset of action, bridging therapy may be needed.

⁴⁹ Prior to Amendment 8, this sentence had read: "...should be continued..." (See Section 13.2.2)

⁵⁰ Section revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁵¹ Text deleted as per Amendment 6. (See Section 13.1.2)



If therapeutic anticoagulation is required, subjects should start therapeutic anticoagulation immediately, irrespective of the timing of the last dose of study rivaroxaban.

6.9.4 Proton pump inhibitor treatment - amended

Subjects who develop a continuous⁵² need for treatment with a proton pump inhibitor during the study⁵² (e.g., gastroduodenal ulcer) should discontinue study pantoprazole/pantoprazole placebo while receiving non-study proton pump inhibitor treatment. Study pantoprazole/pantoprazole placebo should⁵² be restarted in all subjects who no longer have a continuous⁵² need for proton pump inhibitor therapy.

7. Procedures and variables

7.1 Schedule of procedures

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. Further details are provided in the Manual of Operations.

A tabulated overview ([Table 7-1](#)) of the procedures conducted in each of these periods is provided in [Section 7.1.1](#) and the procedures and their timing are described in more detail in [Section 7.1.2](#).

⁵² Text modified/added as per Amendment 6. (See [Section 13.1.2](#))

7.1.1 Tabulated overview - amended

Table 7–1. Schedule of evaluations

Visit	Pre-Screening ^a	Screening/ Run-in	Randomization ^{s,53}	Follow-up															Washout
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Wash out	
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m	
Windows ^{a,53}			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d	
Informed consent (if required for pre-screening)	X																		
Informed consent		X ^{r,53}																	
Inclusion/exclusion criteria	X	X	X ⁵³																
Demographics		X																	
Medical history			X																
Physical measurements ^b		X							X								X		
Concomitant medications		X	X						X								X		
Pregnancy test if pre-menopausal		X																	
Laboratory tests ^c		X ^d	X ^e																
Blood/DNA collection and storage			X ^f	X ^f															

⁵³ Added as per Amendment 6. (See Section 13.1.2)

	Pre-Screening ^a	Screening/ Run-in	Randomization ^{s,53}	Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Wash out
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m
Windows ^{q,53}			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d
Diet and activity questionnaires		X ^o	X ^o	X ^{p,54}						X								
MoCA, DSS, and SAGE ^{t, 55}		X ^o	X ^o	X ^{p,54}						X								X
EQ-5D ^g		X ^o	X ^o	X ^{p,54}						X								X
Health Care Costs			X															
Driving Status			X															
EuroSCORE for subjects randomized post CABG surgery			X															
CT coronary angiography ^h								X ^h										
MRI brain ⁱ			X															X
Outcomes			X ⁵⁴	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
Study drug dispensed		X ^k	X ⁱ			X		X	X	X	X	X	X	X	X	X		
Study drug adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug accountability			X	X		X		X	X	X	X	X	X	X	X	X	X	

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

⁵⁴ Added as per Amendment 6. (See Section 13.1.2)

⁵⁵ Footnote t added as per Amendment 8 (See Section 13.2.2)

- 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 4-7⁵⁶ 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 year⁵⁶ prior.
- e. Repeat serum creatinine in patients being enrolled Day 4-7⁵⁶ 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.⁵⁶
- f. Collection of blood & DNA samples for central evaluation in subjects participating in the COMPASS-MIND substudy is optional. If collected, obtain samples⁵⁶ at randomization, before starting the study drug⁵⁶, and at 1 month, or as close to one month after randomization as possible.⁵⁶ 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.⁵⁶
- 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 event⁵⁷
- h. CT angiography will be performed at 1 year or later in all subjects who are randomized Day 4-7⁵⁶ 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.^{56, 57}
- i. MRI of the brain will be performed only in COMPASS-MIND substudy subjects after randomization^{56, 57} 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.⁵⁶ Dispense run-in medications. CABG surgery patients will be randomized Day 4-7⁵⁶ 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”).⁵⁶
- 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.⁵⁶
- 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.⁵⁶

⁵⁶ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁵⁷ Text modified/added as per Amendment 8. (See Section 13.2.2)

- r. CABG subjects can sign the informed consent before or after surgery.⁵⁶
- 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

7.1.2 Timing of assessments

7.1.2.1 Pre-screening visit

Pre-screening visits are optional but when performed will generally be conducted during the 1-2 months prior to screening and run-in. The aim of the pre-screening visit is to establish subject eligibility. Some centers may be required by the local ethics committee to obtain informed consent prior to conducting pre-screening events. If this is the case, pre-screening activities will include:

- Obtain written informed consent for pre-screening (if required)
- Review inclusion and exclusion criteria and evaluate subject willingness to participate in the study
- Record adverse events if informed consent was obtained

7.1.2.2 Screening and run-in visit(s) - amended

The aim of the screening visit is to confirm eligibility. Laboratory results of creatinine and total cholesterol performed within a year of this visit can be used to assess eligibility. Otherwise, obtain relevant laboratory tests.⁵⁸ For subjects who are randomized Day 4-7⁵⁸ after CABG surgery, the screening visit may be performed prior to or after⁵⁸ surgery (Section 4.1.1).⁵⁹ Screening/run-in activities include:

- Obtain written informed consent
- Review inclusion and exclusion criteria and evaluate subject willingness for participation in the study
- Collect demographic data: gender, date of birth, race/ethnicity
- Measure body weight (kg or lb), height (cm or in), waist circumference (cm or in), hip circumference (cm or in), heart rate (bpm), ankle-brachial blood pressure index (mm Hg)
- Record concomitant medications
- 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

⁵⁸ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁵⁹ Text deleted as per Amendment 6. (See Section 13.1.2)



Visit. (In patients randomized Day 4-7 post CABG, the questionnaires should be performed at the 1 month visit).⁶⁰

- Conduct pregnancy test (serum or urine) for premenopausal subjects
- Record adverse events
- Stop treatment with non-study aspirin
- Obtain medication code for run-in study treatment and dispense run-in study medications (not applicable for subjects who are randomized Day 4-7⁶⁰ after CABG surgery)

A subject can be re-screened/re-run-in, if not previously randomized to study treatment.⁶⁰

- Obtain written informed consent, if applicable⁶⁰
- Repeat/complete the rest of the screening/run-in activities, where applicable.⁶⁰

7.1.2.3 Randomization visit (Day 0 ± 5 days) - amended

The aim of the randomization visit is to assign blinded study treatment. Subjects may be randomized if they fulfill all study inclusion and exclusion criteria, have the blood results of the serum creatinine and total cholesterol available within 3 months of this visit, have at least⁶⁰ 80% adherence (except for extenuating circumstances)⁶⁰ to both run-in study treatments and remain committed to participate in the trial and randomization activities including:

- Perform run-in drug accountability; assess adherence to run-in drug (not applicable for subjects who are randomized Day 4-7⁶⁰ after CABG surgery)
- Record disease and surgical history
- Record concomitant medications
- Administer diet and activity questionnaires (may be administered at Screening/Run-in instead of Randomization)
- Administer MoCA, DSS, and SAGE questionnaires (may be administered at Screening-Run-in instead of Randomization).
- Administer EQ-5D questionnaire (may be administered at Screening/Run-in instead of Randomization).

⁶⁰ Text modified/added as per Amendment 6. (See Section 13.1.2)



- In patients randomized day 4-7 post CABG perform questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) at 1 month visit⁶¹
- Collect health care costs information
- Assess driving status
- Assess local laboratory results of creatinine and total cholesterol⁶¹
- Collect blood for local laboratory assessment of creatinine in subjects being randomized post CABG
- Collect EuroSCORE for subjects being randomized post CABG surgery (if score is not available in medical chart, calculate EuroSCORE)
- Collect blood (DNA) sample for storage and central evaluation in COMPASS MIND substudy subjects, if applicable⁶¹
- MRI of the brain will be performed only in COMPASS-MIND substudy subjects after randomization⁶²
- Record outcomes⁶¹
- Record adverse events
- Randomize subject by accessing the PPD randomization and drug management system
- Dispense assigned study treatments. Study treatments should be started on the day of randomization or, if study aspirin has already been administered on the day of randomization, study treatment should be started the day thereafter.

7.1.2.4 Follow-up visits

7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+) - amended

Subjects will be seen in the clinic at Month 1 (± 7 days), Month 6 (± 4 weeks), and thereafter at 6 month intervals (± 4 weeks) post-randomization until Visit 15. Thereafter, subjects will continue to be seen at the clinic every 6 months until the required number of primary efficacy outcomes has been collected. During the first year, subjects will be phoned at Month 3 and Month 9 to assess and encourage adherence to study treatments, and a further phone call (End

⁶¹ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁶² “after randomization” was added as per Amendment 8. (See Section 13.2.2)

of Washout Telephone Visit) will be made 30 days after the Final Follow-up Visit to assess outcomes and adverse events. Follow-up assessments include:

- Record outcomes
- Record adverse events (if appropriate, complete the Hospitalization CRF to allow collection of medical resource utilization [MRU] data)
- In patients randomized day 4-7 post CABG perform questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) (1 month).⁶³
- Collect blood sample for storage and central evaluation in COMPASS MIND substudy subjects at Visit 3 (1 month)
- Dispense study drug at Visits 5 and 7-15 by obtaining medication numbers through the PPD randomization and drug management system.
- Assess adherence to study drug
- Perform study drug accountability (pill count) at each in-clinic visit
- Perform CT angiography only at Visit 7 (1 year or later if not performed at 1 year) in all subjects who are randomized during the first week after CABG to evaluate graft patency (except in subjects 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.⁶³
- Additional assessments to be performed only at Visit 9 (2 years) include:
 - Physical measurements: body weight (kg or lb), height (cm or in), waist circumference (cm or in), hip circumference (cm or in), heart rate (bpm), ankle-brachial blood pressure index (mm Hg)
 - Record concomitant medications
 - Administer diet and activity questionnaires at Visit 9⁶⁴
 - Administer MoCA, DSS, and SAGE questionnaires
 - Administer EQ-5D questionnaire

⁶³ Text added as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁶⁴ Text deleted as per Amendment 6. (See Section 13.1.2)



While every effort should be made for the subject to attend those visits that are meant to be in person, infrequently it may not be possible to conduct the visit in person in which case the visit may occur by telephone instead.⁶⁵

7.1.2.4.2 Non-clinic assessments (Months 3 and 9 ± 4 weeks)

At Months 3 and 9, the study staff will contact the study subject by telephone to collect the following data:

- Record outcomes
- Record adverse events
- Discuss study drug adherence

Additional interim phone calls or visits may occur as required to appropriately manage subjects during the study. Further details are included in the Manual of Operations.

7.1.2.4.3 Final Follow-up Visit (± 4 weeks)

When the required number of primary efficacy outcomes have been collected, the study termination will be announced and subjects will return to the clinic for a Final Follow-up Visit. Final follow-up assessments include:

- Physical measurements: body weight (kg or lb), height (cm or in), waist circumference (cm or in), hip circumference (cm or in), heart rate (bpm), ankle-brachial blood pressure index (mm Hg)
- Record concomitant medications
- Administer MoCA, DSS, and SAGE questionnaires
- Administer EQ-5D questionnaire
- MRI of the brain will be performed only in COMPASS-MIND substudy subjects
- Record outcomes
- Record adverse events (if appropriate, complete the Hospitalization CRF to allow collection of MRU data)
- Assess adherence to study drug

⁶⁵ Sentence added as per Amendment 8. (See Section 13.2.2)



- Perform study drug accountability (pill count)

7.1.2.5 End of washout telephone visit (30 days post Final Follow-up Visit \pm 5 days)

The washout visit will be conducted by study staff via telephone interview. Washout visit assessments include:

- Record outcomes
- Record adverse events (if appropriate, complete the Hospitalization CRF to allow collection of MRU data)

7.2 Population characteristics

7.2.1 Demographics

Demographic data will be collected at the Screening Visit. These data will include:

- Gender
- Date of birth
- Race/ethnicity

7.2.2 Medical history

Medical history (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Medical history parameters to be collected at randomization will include, e.g.:

- Disease history associated with CAD or PAD (myocardial infarction, angina, intermittent claudication, diabetes, renal dysfunction, heart failure, transient ischemic attack, stroke, liver disease, hypertension, cancer, bleeding requiring transfusion, tobacco use) or associated with gastrointestinal disease (bleeding, erosions, ulceration, obstruction, perforation)



- Surgical history associated with CAD or PAD (coronary percutaneous transluminal coronary angioplasty, atherectomy, percutaneous coronary intervention, coronary artery bypass graft, peripheral artery bypass surgery, peripheral percutaneous transluminal angioplasty, limb or foot amputation) or associated with gastrointestinal disease (bleeding, erosions, ulceration, obstruction, perforation)

7.2.3 Other baseline characteristics - amended

Validated health and quality of life questionnaires (SAGE, MoCA, DSS, and EQ-5D) will be administered at screening/run-in or randomization, or as soon as possible thereafter, at Month 24 and at the Final Follow-up Visit, and at the next study clinic visit after each outcome event to measure the effect of randomized treatment on functional outcomes and quality of life.

Diet and activity questionnaires will also be administered at screening/run-in or randomization, or as soon as possible thereafter, and at Month 24 in order to explore the determinants and consequences of cognitive decline in patients with CAD and PAD. These inventories may be administered at the beginning of each of these study visits prior to meeting with the physician and prior to the conduct of any other visit-related procedures.⁶⁶

7.3 Efficacy - amended

The primary efficacy outcome is a composite of myocardial infarction, stroke, or cardiovascular death.

The secondary efficacy outcomes are:⁶⁷

- a) A composite of coronary heart disease death, myocardial infarction, ischemic stroke or acute limb ischemia
- b) A composite of cardiovascular death, myocardial infarction, ischemic stroke or acute limb ischemia
- c) Mortality by any cause

Other efficacy outcomes include the evaluation of responses recorded for the SAGE, MoCA, DSS, and EQ-5D inventories and the following: individual components of the primary and secondary outcomes, hospitalization, revascularization, amputation, stent thrombosis, unstable angina, worsening angina, new angina, heart failure, resuscitated cardiac arrest, venous thromboembolism, new diagnosis of cancer, MRU, coronary artery bypass graft failure.⁶⁷

Hospitalization data will be collected on the CRF to permit the analysis of MRU. These data will be analyzed and reported to the sponsor separately and will include:

⁶⁶ Section was modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁶⁷ Revised with Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

- Total days length of stay
- Emergency room visits
- Intensive care unit /cardiac care unit days
- Rehabilitation and skilled nursing facilities
- Reason for medical resource use, i.e., major adverse cardiovascular event or bleeding

MRU data will be incorporated into economic modeling, which will be performed and reported separately from this study.

The outcome for the pantoprazole randomization is a composite of 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, and gastrointestinal obstruction, or perforation.⁶⁸

7.4 Pharmacokinetics / pharmacodynamics

No measures of pharmacokinetics or pharmacodynamics will be performed for this study.

7.5 Safety

The primary safety outcome is Modified ISTH major bleeding, defined as: i) fatal bleeding, and/or ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring re-operation and/or iii) bleeding leading to hospitalization.

The known side effect profile of rivaroxaban can be found in the Investigator Brochure (IB), which is updated on a regular basis. Any new, relevant information about side effects of rivaroxaban will be provided to the subject by the investigator or designate.

7.5.1 E6 Definition of (serious) adverse event - amended

An AE is any untoward medical occurrence including an exacerbation of a pre-existing condition or abnormal laboratory finding in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

⁶⁸ Text deleted as per Amendment 6. (See Sections [13.1.2](#))

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity is a congenital anomaly / birth defect and/or is another medically important serious event representing a significant hazard, which is comparable to the aforementioned criteria.⁶⁹

Note: If a subject is hospitalized or has a procedure that was planned or anticipated prior to the subject signing the informed consent, the hospitalization/procedure is considered part of medical history or a therapeutic intervention and is not the result of an (S)AE unless the severity has worsened or changed unexpectedly. Additionally, a procedure is not an (S)AE, but the reason for the procedure may be an (S)AE.⁷⁰

7.5.2 Causal relationship - amended

The assessment of the causal relationship between an AE and the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF. The causality assessment should be done separately for each study treatment as detailed in the CRF. The assessment is based on the question whether there was a “reasonable causal relationship” to the study drug in question.⁷¹

7.5.3 Protocol-specific adverse event definitions

7.5.3.1 Protocol-specific exceptions to SAE reporting - amended

Rivaroxaban has been extensively studied in Phase 2 and 3 clinical studies involving more than 80,000⁶⁹ patients and its overall adverse event profile has been well described. Appropriate information concerning adverse events will be systematically collected and submitted to regulatory authorities and all data on safety and outcomes will be reviewed regularly by an unblinded Data and Safety Monitoring Board.

For the purposes of this trial, the following events will be captured on the CRF as study outcome events only and will be waived from unblinding and will be exempted from the expedited reporting but will be included in the final study report.

- Primary efficacy⁷² outcomes:
 - Cardiovascular death
 - Myocardial infarction

⁶⁹ Text modified as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁷⁰ Paragraph added with Amendment 8. (See Section 13.2.2)

⁷¹ Section 7.5.2 and text within was added in Amendment 6.

⁷² Text modified/added as per Amendment 6. (See Section 13.1.2)



- Stroke
- Secondary and tertiary efficacy⁷³ outcomes
 - Coronary heart disease death
 - Ischemic stroke
 - Acute limb ischemia
 - Cardiovascular hospitalization
 - Venous thromboembolism
 - Revascularization
 - Amputation
 - Stent thrombosis⁷⁴
 - Angina pectoris (unstable, worsening or new)⁷⁴
 - Heart failure
 - Resuscitated cardiac arrest
 - New diagnosis of cancer
 - Coronary artery bypass graft failure⁷⁴

- Primary safety outcomes:⁷⁴

As bleeding, including fatal bleeding, from all tissues and organs is a known side effect of rivaroxaban, bleeding events, including those resulting in hospitalization, will not be reported as (S)AEs, but will be captured on the CRF only, and will be reported as outcomes.

- Expected Events:⁷⁴

In addition, events that are expected to occur with high frequency in the population under study and for which no safety signal arose from more than 80,000^{74, 75} patients already studied in clinical trials with rivaroxaban will be captured on the CRF only, will be waived from unblinding, and be will be exempted from expedited reporting. These include:

⁷³ Text revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁷⁴ Text modified/added as per Amendment 6. Section 7.5.3.2 added. (See Section 13.1.2)

⁷⁵ Number changed from 70,000 to 80,000 as per Amendment 8.

- Planned hospitalizations (e.g., for surgery, respite care)
- Non-cardiovascular SAEs (including unplanned hospitalizations) that are expected to occur with high frequency in the population under study (depression, pneumonia, trauma, chronic obstructive pulmonary disease, diabetes mellitus)

7.5.3.2 Reporting of (S)AEs - amended

The following events are to be reported to PPD on the SAE/ESI CRF within 24 hours of the investigator becoming aware of the event/diagnosis.⁷⁴ Bayer HealthCare Global Pharmacovigilance⁷⁴ is responsible for reporting these events to the health authority:⁷⁴

- Any non-cardiovascular death of a subject occurring after signing informed consent or prior to the end of monitoring for adverse events. (note: fatal bleeding events are primary safety outcomes and are exempted)⁷⁴
- Any non-cardiovascular SAEs not listed in Section 7.5.3.1
- Any non-cardiovascular AE that recurs when the subject is restarted on study drug (positive re-challenge).⁷⁴

In addition, any AEs of particular concern to the investigator may be recorded on the CRF to bring them to the attention of the sponsor.

7.5.3.3 Adverse events of special safety interest - amended

For ongoing pharmacovigilance, the large COMPASS trial is an opportunity to identify rare events in the population that may or may not be drug-related. The following events have, to date, not been observed with increased frequency with rivaroxaban, but are considered AEs of special safety interest. These events must be reported to PPD, independent of their seriousness, but within the same timelines as an SAE (within 24 hours) by reporting them on the SAE page of the CRF. Bayer HealthCare Global Pharmacovigilance may decide to upgrade the event based on the information received.

- Pregnancy outcome and any congenital anomaly⁷⁶
- Events currently under observation by Bayer HealthCare Global Pharmacovigilance and which may be unusual in the absence of drug therapy in the study population. The types of events that fall into this category are listed in Table 7-2.
- Events of special interest that are mild or moderate do not need to be reported in expedited fashion

⁷⁶ Text deleted as per Amendment 6. (See Section 13.1.2)

**Table 7–2. Adverse events of special interest**

System Organ Class	Example
Blood and lymphatic system	Pancytopenia, aplastic anemia Red cell aplasia Agranulocytosis Severe leukopenia Severe neutropenia Severe thrombocytopenia (<50 x 10 ⁹ /L) Thrombotic thrombocytopenic purpura Immune thrombocytopenic purpura Heparin-induced thrombocytopenia Hemolytic anemia Severe megaloblastic anemia Disseminated intravascular coagulation
Skin and subcutaneous disorders	Severe exfoliative dermatitis Severe bullous skin reactions Erythema multiforme Stevens Johnson Syndrome Toxic epidermal necrolysis Epidermolysis Anaphylaxis Angioedema requiring hospitalization Angioneurotic oedema (not otherwise explained e.g. by ACE-inhibition) Allergic vasculitis
Hepatobiliary disorders	Hepatic failure (incl. fulminant hepatitis, hepatic necrosis) and associated disorders (like hepatorenal syndrome, encephalopathy) Severe hepatocellular damage and hepatitis Jaundice (if unrelated to gallstones)
Gastrointestinal disorders	Pancreatitis Retroperitoneal fibrosis Pseudomembraneous colitis
Renal and urinary disorders	Acute nephritis (not caused by infection) Nephrotic syndrome Acute renal failure (only if not related to cardiovascular event or bleeding)
Nervous system disorders	Acute polyneuropathies
Muscle disorders	Rhabdomyolysis Toxic myopathy
Respiratory disorders	Alveolitis Acute interstitial pneumonia
Infections	Severe sepsis
Endocrine disorders	Adrenal insufficiency Addison's disease
Eye and ear disorders	Acute, sudden vision loss or acute reduced visual acuity (only if not related to stroke) Sudden hearing loss
Cardiac disorders	Torsades de pointe

7.5.3.4 Non-serious adverse events

With the exception of the events of special interest defined in Section 7.5.3.3, AEs which are not serious but which lead to permanent discontinuation of study medication will be captured in the CRF but do not require expedited reporting.

Non-serious AEs which do not lead to discontinuation of study medication will not be collected.

7.5.3.5 Pregnancies - amended

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in the study subject's partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form.⁷⁷ For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all pregnancy reports, the forms provided by PPD are to be used.⁷⁸

7.5.4 Reporting of events to Bayer by PPD and compliance with regulatory authorities' reporting requirements - amended

Adverse events that require expedited reporting described in Sections 7.5.3.2, 7.5.3.3, and 7.5.3.5⁷⁷ (protocol-specific adverse event reporting) are to be recorded on the appropriate SAE CRF page and are to be forwarded to PPD within 24 hours of the investigator having been made aware of the event. In this trial, exempted outcomes are to be recorded on the appropriate outcome CRF page, not the SAE CRF page.⁷⁷ Upon receipt of an SAE CRF page⁷⁷ this form will be reported to Bayer Global Pharmacovigilance by PPD within 24 hours, or 3 calendar days for weekends or public holidays, or next working day whichever is earlier.

All required information will be listed on the SAE page in the CRF. If the required information is not immediately available, PPD will query the center to obtain the information once it becomes available. In the rare circumstances that additional information is needed, PPD will work with Bayer and the site investigators to obtain additional information in a timely manner to enable Bayer to comply with regulatory authorities' reporting requirements.

⁷⁷ Text modified/added as per Amendment 6. (See Section 13.1.2)

⁷⁸ Section 'Data Safety Monitoring Board' was deleted in Amendment 6. (See Section 13.1.2)



7.6 Other procedures and variables

No other procedures will be conducted and no other variables will be explored in this trial.

7.7 Appropriateness of procedures / measurements

With the exception of routine laboratory assessments performed at screening, imaging studies performed in subjects randomized post CABG, and blood and imaging studies in those participating in the COMPASS MIND substudy, no invasive procedures are planned for this study. All study visits will be used to collect safety and outcome data, which are appropriate measures for this events-driven trial.

8. Statistical methods and determination of sample size

8.1 General considerations

General description of the statistical methods is outlined below. A more detailed statistical analysis plan (SAP) will be provided in a separate document.

The core SAP document will provide a more technical and detailed elaboration of the principal features of the planned analyses, e.g. censoring schemes for time-to-event variables. The core SAP will be finalized ideally prior to study enrollment, at the latest before any substantial information in the trial has accumulated.

Amendments and/or appendices to the core SAP will 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 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 from the trial.

Analyses will be performed using SAS software (SAS Institute Inc, Cary, NC, USA).

8.2 Analysis sets and data scopes

8.2.1 Analysis sets

Intention-to-treat analysis set

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline,⁽³¹⁾ will include all randomized subjects.

Safety analysis set (for secondary safety analyses)

The safety analysis set will include all randomized subjects who received at least one dose of study medication.

8.2.2 Data scopes

Data scope according to intention-to-treat principle

Analyses according to the intention-to-treat principle will be based on the intention-to-treat analysis set and will include all outcome events observed from randomization until the date of the Final Follow-up Visit for each subject. For subjects who are unable to attend the Final Follow-up Visit within the acceptable closeout time-window (range of dates depending on date of announcement of study termination), a calendar date will be chosen after which events will not be counted for primary analysis before unblinding. 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

Additional analyses of safety outcomes will be based on the safety analysis set. 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 the date of the Final Follow-up Visit or a chosen calendar date described above for each subject
- All outcome events observed from randomization until 2 days following permanent discontinuation of the study drug (“treatment emergent outcomes” analysis)
- All outcome events observed from randomization up to 30 days following permanent discontinuation of the study drug
- All outcome events observed from randomization during the entire follow-up and wash-out periods

8.3 Variables - amended

Time (in days) from randomization to the first occurrence of

- the primary, secondary, tertiary efficacy outcomes (except SAGE, MoCA, DSS, and EQ5D, and MRU) for the antithrombotic treatment randomization (Sections [8.3.1](#), [8.3.2](#), [8.3.3](#)),
- the primary safety outcome for the antithrombotic treatment randomization (Section [8.3.4](#)), and



- the outcome for the pantoprazole randomization (Section 8.3.5)

will be analyzed as time-to-event variables.

8.3.1 Primary efficacy outcome

The primary efficacy outcome is the composite of the following outcomes:

- Myocardial infarction
- Stroke
- Cardiovascular death

8.3.2 Secondary efficacy outcomes - amended

⁷⁹The secondary efficacy outcomes are (in the following order):

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

8.3.3 Tertiary and other efficacy outcomes - amended

The tertiary efficacy outcomes are:

- Subject-reported SAGE, MoCA, DSS, and EQ-5D
- Individual components of the primary and secondary outcomes
- Hospitalization for cardiovascular reasons⁸⁰
- Hospitalization
- Revascularization⁸⁰
- Amputation⁸¹
- Stent thrombosis⁷⁹
- Unstable angina
- Worsening angina
- New angina

⁷⁹ Text modified/added as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

⁸⁰ Added as per Amendment 8. (See Section 13.2.2)

⁸¹ Text deleted as per Amendment 6. (See Section 13.1.2)



- Heart failure
- Venous thromboembolism⁸⁰
- Resuscitated cardiac arrest
- New diagnosis of cancer
- MRU
- Coronary artery bypass graft failure⁸²

8.3.4 Primary safety outcome

The primary safety outcome is modified ISTH major bleeding, defined as:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring reoperation, and/or
- bleeding leading to hospitalization

8.3.5 Outcome for pantoprazole randomization - amended

The outcome for the pantoprazole randomization 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 gastrointestinal origin with documented decrease in Hb of 2 g/dL⁸³
- Symptomatic gastroduodenal ulcer
- Gastrointestinal pain with underlying multiple gastroduodenal erosions, obstruction or perforation

8.3.6 Subgroup variables - amended

Homogeneity of treatment effect will be examined for the following subgroup variables:

- CAD⁸² (yes, no)
- PAD⁸² (yes, no)
- CAD and PAD (yes, no)

⁸² Text modified as per Amendment 6. (See Section 13.1.2)

⁸³ Text deleted as per Amendment 6. (See Section 13.1.2)



- CAD only, PAD only, CAD and PAD
- CABG days 4-7 before randomization⁸² (yes, no)
- Any prior CABG (yes, no), further subdivided as CABG days 4-7 before randomization and other prior CABG⁸⁴
- 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)

Additional subgroup variables, if identified, will be specified in the SAP prior to unblinding of the treatment assignment.

8.4 Statistical and analytical plans - amended

Summaries by randomized group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. Mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

Testing strategy⁸⁵

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 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

⁸⁴ Bullet was added as per Amendment 8. (See Section 13.2.2)

⁸⁵ Testing strategy text added as per Amendment 8. (See Section 13.2.2)

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 1, these logical restrictions are represented by arrows.

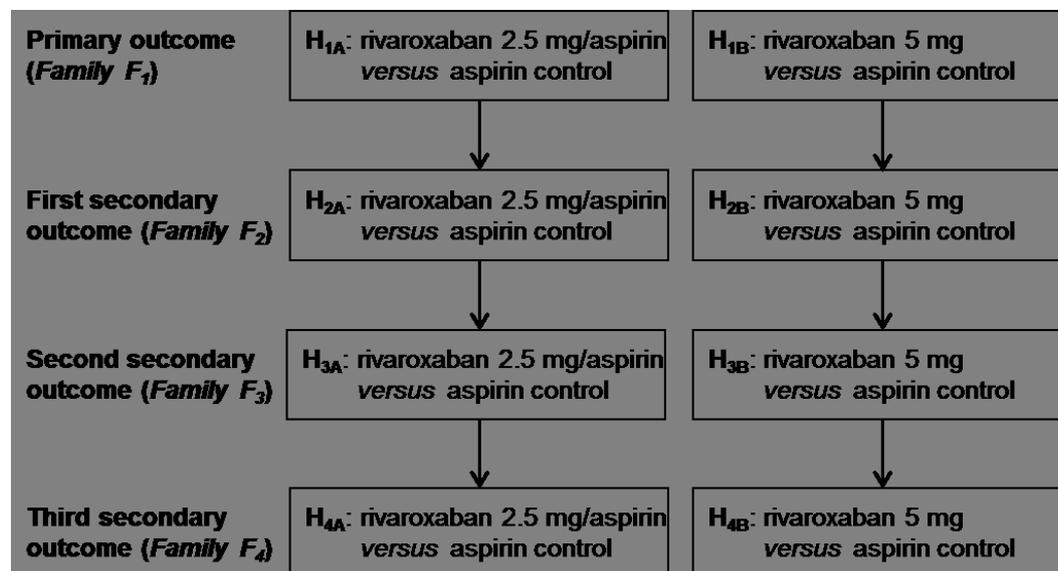


Figure 1: Hypothesis testing problem

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 (33,34) was recently proposed in Brechenmacher et al. (32). Details for the setting of this study will be described in the SAP.

8.4.1 Analysis of the primary efficacy outcome - amended

Analysis of the primary efficacy outcome will be based on the intention-to-treat principle (Section 8.2). 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).

Each of the primary null hypotheses $H_{0,riva2.5}$ and $H_{0,riva5}$ stating that “there is no difference between the considered rivaroxaban-based treatment group and the aspirin control group in the probability of the primary efficacy outcome for all time points” will be tested against the respective alternative hypotheses $H_{1,riva2.5}$ and $H_{1,riva5}$ stating that “there is a difference

between the two groups in the probability of the primary efficacy outcome for at least one time point”.

The 2 comparisons will be performed using 2 separate stratified log-rank tests. Following the mixture gatekeeping procedure as mentioned in Section 8.4, a truncated Hochberg test with the pre-specified truncation parameter $\gamma = 0.9$ at $\alpha=0.05$ will be used. Further details will be described in the SAP. 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. Study center will not be used as a stratification factor. 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.⁸⁶

Kaplan-Meier estimates of cumulative risk and 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).

Hazard ratio, relative risk reduction, and corresponding 2-sided 95% confidence intervals will be estimated based on 2 separate stratified Cox proportional hazards models. Censoring will be assumed independent of the randomized group assignment. 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 of time for evidence of non-parallelism and the smoothed plot of the scaled Schoenfeld residuals to directly visualize the log hazard ratio,⁽³³⁾ 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. Further details will be specified in SAP.

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.⁸⁷

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 as described in Section 8.4.5. Further details of this analysis will be specified in SAP.

8.4.2 Analysis of the secondary efficacy outcomes - amended

Analysis of the secondary efficacy outcomes will be based on the intention-to-treat principle (Section 8.2) and will use a similar approach as described in Section 8.4.1. The family-wise

⁸⁶ Paragraph was revised as per Amendment 8. (See Section 13.2.2)

⁸⁷ Text was deleted from this paragraph as per Amendment 8. (See Section 13.2.2)

error rate will be controlled using the truncated and/or regular Hochberg tests as described in Section 8.4 and more detailed in the SAP.⁸⁸

8.4.3 Analysis of the tertiary efficacy outcomes

Analysis of the tertiary efficacy outcomes will be based on the intention-to-treat principle (Section 8.2) and will use a similar approach as described in Section 8.4.1 (except for SAGE, MoCA, DSS, and EQ5D). Analysis of subject reported SAGE, MoCA, DSS, and EQ5D will be described in the SAP. 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. Additional exploratory analyses will be conducted, as described in the SAP.

The MRU data will be incorporated into economic modeling, which will be performed and reported separately from this study.

8.4.4 Analysis of the primary safety outcome

The principal analysis of the primary safety outcome will be based on the intention-to-treat principle (Section 8.2). The analysis will follow similar methodology as the analysis of the primary efficacy outcome described in Section 8.4.1.

In addition, the primary safety outcome will be analyzed based on the other data scopes defined in Section 8.2.2.

8.4.5 Analysis of the outcome for pantoprazole randomization - amended

Analysis of the outcome for pantoprazole randomization will be based on the intention-to-treat principle (Section 8.2) and will include all subjects randomized to receive pantoprazole 40 mg od or pantoprazole placebo.

Pantoprazole 40 mg od treatment group and 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 outcome⁸⁹ 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 outcome⁸⁹ for at least one time point”.

The comparison will be performed using a log-rank test stratified by antithrombotic therapy study group (3 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.

⁸⁸ Paragraph was revised as per Amendment 8. (See Section 13.2.2)

⁸⁹ Text deleted as per Amendment 6. (See Section 13.1.2)

Kaplan-Meier estimates of cumulative risk and cumulative hazard functions will be provided to evaluate the timing of event occurrence in the 2 proton pump inhibitor study groups and the consistency of the treatment effect for all time points (the 2 survival curves do not cross).

Hazard ratio, 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 8.4.1 will be used for assessing the plausibility of the proportional hazards assumption.

In addition, joint effect and interaction between the antithrombotic and pantoprazole study groups 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 2 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 2 factors.

If the interaction term is significant at the 5% type I error level, then the interaction ratio test (36) will be performed to assess synergy and sub-additivity of the two treatment effects. Additional exploratory analyses, 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, will be conducted as described in the SAP.

8.4.6 Subgroup analyses - amended

Subgroup analyses for the primary efficacy and safety outcomes, and the outcome⁹⁰ for pantoprazole randomization will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes (Sections 8.4.1, 8.4.2, 8.4.3, 8.4.4, and 8.4.5).

Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable (Section 8.3.6) and the corresponding treatment-subgroup interaction to the respective stratified Cox proportional hazards model

⁹⁰ Text deleted as per Amendment 6. (See Section 13.1.2)



used in the main analysis. Cox proportional hazards regression model (not stratified) will be used for baseline proton pump inhibitor use (yes, no) variable.

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 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. 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(37) 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),(38) 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.(38)

Following the test of interaction, hazard ratio and relative risk reduction 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.

8.4.7 Handling of missing data

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.

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).⁽³⁹⁾

8.5 Planned interim analyses - amended

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.

Two formal interim analyses are planned when 50% and 75% of the expected number of accumulated primary efficacy outcome events accrue.

If the interim analyses show clear and consistent benefit in both treatment arms, the DSMB may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping: a reduction of 4 standard deviations in the analysis of the primary efficacy outcome at the first interim analysis or 3 standard deviations at the second interim analysis. If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be done after at least 4-6 months 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 8.4.1 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:⁹¹

- If one intervention was stopped early for efficacy, the multiple testing procedure for the final analysis will be performed as described in Section 8.4 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.
- If one intervention was stopped early for futility, the final analysis will be performed when at least 1,513⁹² subjects in the 2 remaining arms have experienced an event.

⁹¹ The details in the bulleted paragraphs were added as per Amendment 8. (See Section 13.2.2)

⁹² The whole study was planned to be stopped when at least 2,200 subjects had experienced a primary outcome event. Under the planning assumptions that both alternative hypotheses are true, observed randomization times

The final analysis will be performed according to the multiple testing strategy as described in Section 8.4. 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 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-quarter⁹³ subjects with PAD; this will be monitored during the trial and steps may be taken to adjust the proportion during the trial.

8.6 Determination of sample size - amended

⁹⁴In this trial, it is planned to randomize at least 27,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome.

The aim is to achieve at least 90% power to detect a 20% relative risk reduction (RRR) for each of the 2 rivaroxaban-based treatment groups vs. the common aspirin control group. The total number of events needed is shown in Table 8-1 for different scenarios depending on the assumed annual incidence rate for the primary outcome in the aspirin group based on the assumptions modified according to Amendment 6 (integrated protocol Version 2.0), dated 03 JUL 2014. Due to the event-driven study design, the number of randomized subjects, length of enrollment and total study duration may vary. If recruitment is going extremely well, a larger number of subjects may be recruited. All numbers below 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-arm study with 1:1:1 randomization
- In total, a minimum of 21,400 subjects are randomized (approximately 7,134 subjects per treatment group) according to a 1:2:3:4:4 pattern within 2.5 years

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.

⁹³ Prior to Amendment 8, this was one-third subjects with PAD.

⁹⁴ This section was revised as per Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)



- 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%
- Constant annual incidence rate in aspirin control group between 3.0% and 4.0%
- 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 about 2.5 years
- Early discontinuation of study drug: about 6% and 4% in the 1st and 2nd 6-month periods, 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 8–1](#).

Table 8–1. Events calculations

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 and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban arms with at least 90% power, it was planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome. In this multi-center study, each center is expected to randomize at least 50 subjects.

The originally planned sample size of 21,400 and 5 year study duration was based on an annual primary incidence rate in the control group of 3.5% and 90% power to detect a relative risk reduction of 20% in each of the rivaroxaban arms. Based on an observed incidence rate of 2.9% as of July 2015, it is now planned to randomize at least 27,400⁹⁵ subjects. This new sample size will maintain current study timelines and 90% power to detect a 20% relative risk reduction in each of the rivaroxaban arms, based on the following revisions to the original assumptions:

- Overall length of recruitment period about 3 to 3.5 years and taking observed randomization times up to July 2015 into account

⁹⁵ Text modified as per Amendment 6. (See Section [13.1.2](#))



- 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, resulting in a constant incidence rate of about 3.3% per year for the aspirin control group assuming a 20% relative risk reduction for both hypotheses
- Censoring due to non-CV death at an event rate of almost 1% per year

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 subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in 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 Final Follow-up Visit for each subject

Under these assumptions, the expected total number of major upper gastrointestinal complications is between 570 and 780, depending on the observed event 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(40) implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis System (SAS) macro provided by J. Shih (1995).(41) In addition, simulations were performed to confirm that the mixture gatekeeping procedure as described in Section 8.4 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).



9. Data handling and quality assurance

9.1 Data recording

All data will be managed centrally at the PPD [REDACTED]. Case report forms will be completed electronically using iDataFax or will be collected on paper CRF and faxed to PPD [REDACTED] for integration into iDataFax. All data will be kept secure and confidentiality of all study subjects will be carefully protected.

Further details are included in the Manual of Operations.

9.2 Monitoring

In accordance with applicable regulations, GCP, and PPD [REDACTED] procedures, Site Management Coordinators and PPD [REDACTED] project office staff will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor will develop a Study Oversight Plan to ensure appropriate oversight of the study. Additionally, risk-based monitoring will be implemented for this study and further details will be included in the Site Management Coordination Plan.

PPD [REDACTED] is responsible for the monitoring of the study. The purpose of monitoring is to verify that the data and study procedures have been conducted as described in this protocol and to ensure the validity of the study results. Study monitors will follow the Site Management Coordination Plan to verify that:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met

Monitoring will encompass a variety of methods at the central, national, and site levels; incorporate central data verification, national event verification, and local site monitoring; focus on key aspects of the study; and involve multiple levels of oversight to enable rapid and efficient identification and correction of issues that arise. Both the NL and PPD [REDACTED] will perform central monitoring with close communication between PPD [REDACTED] the NL, the Sponsor, and the sites. Additionally, the NL will also oversee focused on-site monitoring visits to maintain the quality and integrity of the data. Signed informed consent will be verified to ensure that



consent has been obtained and a sample of the cases will be reviewed to ensure that study procedures have been followed.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor, auditors, and inspectors direct access to all relevant documents.

9.3 Data processing – amended

Data that may be directly recorded on the CRFs (ie., no prior written or electronic record of data) and can be considered to be source data are:

- Medical history (excluding eligibility criteria)
- Adherence
- Demographic data
- Vital signs
- Anthropometric measurements
- Concomitant medications
- Visit attendance⁹⁶
- Pill counts
- Dietary and exercise assessment
- SAGE questionnaire responses
- Adverse events

All other data entered into the CRFs (including all data associated with the primary endpoints for the rivaroxaban and pantoprazole randomizations, as well as SAEs) must be supported by source documentation whether entered at the same time that it is collected by the person performing the assessment, or at a later time following the visit.

The CRFs and iDataFax software will be provided for each participating center along with the study aids. Some sites will complete a paper CRF (instead of the electronic CRF) and submit the data to PPD by fax transmission. At each subject visit, the investigator or research nurse will submit the data to PPD for data management.

⁹⁶ Added with Amendment 8. (See Section 13.2.2)

Clinical data management will be performed in accordance with agreed standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g., the PPD randomization and drug management system, laboratory, events committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's QA department may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. A representative from the PPD QA department may join the audit. The investigator/institution will be informed of the audit outcome. In addition to sponsor audits, with prior agreement from the sponsor, PPD may choose to also conduct audits and will coordinate with the sponsor to select appropriate sites for audit.

In addition, inspections by regulatory health authority representatives and independent ethics committees/institutional review boards (IECs/IRBs) are possible. The investigator should notify PPD (or sponsor) immediately of any such inspection. The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study. The investigator/institution will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection, providing direct access to all related source data/documents. Case report forms and all source documents, including informed consent forms and copies of laboratory and medical test results must be available at all times for review by the authorized clinical study monitor and inspection by health authorities.

9.5 Archiving

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

The confidentiality of all subjects will be protected at both the local centers and at PPD and Bayer. Data at PPD will be kept secure during the study, and for the time that is required by local regulatory requirements after the study. A duplicate copy of the data will be stored securely in a bank vault. At the end of the study, a copy of the data will be provided to the sponsor.

The investigator site file is not to be destroyed without PPD and the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.



10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time for the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
 - Safety findings from this study (e.g. SAEs)
 - Results of any interim analysis
 - Results of parallel clinical studies
 - Results of parallel animal studies
(on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame as agreed upon by the Steering Committee.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

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

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

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

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

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

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.2 Subject information and consent

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

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consentor (if the subject is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data are recorded on study-specific forms).

The investigator will also mention that written approval of the IEC/IRB has been obtained.

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

Only if the subject / legal representative or proxy consentor voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consentor will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution. Any other handling and storage of the signed informed consent statement will be detailed in the ICF.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consentors will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consentor of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

11.3 Publication policy- amended

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. The study results will be reported irrespective of the outcome of the study. The Operations Committee which will also serve as a Publication Committee,⁹⁷ will decide on the authorship of all papers. The main study results will be written by a writing group led by members of the Operations Committee, and may include additional individuals who have made substantial and sustained contributions and will be on behalf of the whole study group.

11.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.5 Confidentiality

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

Only the subject number and patient initials or ‘dummy’ initials will be recorded in the CRF, and all efforts will be made to obliterate subject names that appears on any other document (e.g. pathologist report), before a copy of the document is supplied to PPD or the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that PPD, representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

⁹⁷ Text added as per Amendment 6. (See Section 13.1.2)



12. Reference list - amended

1. Fact sheet: Cardiovascular diseases (CVDs): World Health Organization; 2013. Available from <http://www.who.int/mediacentre/factsheets/fs317/en>⁹⁸
2. WHO. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008b.⁹⁸
3. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001 September 19;286(11):1317-24.
4. Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA* 2006 February 1;295(5):547-53.
5. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL et al. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 2003 April 28;163(8):884-92.
6. Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011 March;105(3):444-53.
7. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012 April 5;366(14):1287-97.
8. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010 December 23;363(26):2499-510.
9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011 September 8;365(10):883-91.
10. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012 January 5;366(1):9-19.
11. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002 January 12;324(7329):71-86.

⁹⁸ Reference modified as per Amendment 6. (See Section 13.1.2)



12. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB, Jr., Lorenz TJ et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 2005 November 16;294(19):2446-54.
13. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996 November 16;348(9038):1329-39.
14. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001 August 16;345(7):494-502.
15. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009 September 10;361(11):1045-57.
16. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007 November 15;357(20):2001-15.
17. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006 April 20;354(16):1706-17.
18. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012 April 12;366(15):1404-13.
19. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol* 2003 February 19;41(4 Suppl S):62S-9S.
20. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J* 2006 March;27(5):519-26.
21. Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007 July 19;357(3):217-27.
22. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011 March 3;364(9):806-17.
23. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000 November 11;321(7270):1183-7.



24. Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011 September;9(9):762-8.
25. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006 August 22;114(8):774-82.
26. Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007 May;28(10):1193-204.
27. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al; COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010 Nov 11;363(20):1909-17
28. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med* 2012 Apr;19;366(16):1489-97.
29. Li C, Hirsh J, Xie C, Johnston MA, Eikelboom JW. Reversal of the anti-platelet effects of aspirin and clopidogrel. *J Thromb Haemost* 2012 April;10(4):521-8.
30. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011 October 4;124(14):1573-9.
31. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med*. 1999;18(15):1905-42.
32. Brechenmacher, T, Xu, J, Dmitrienko, A, Tamhane, AC. A mixture gatekeeping procedure based on the Hommel test for clinical trial applications. *Journal of Biopharmaceutical Statistics*, 2011; 21: 748-767.
33. Dmitrienko, A, Tamhane, AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. *Statistics in Medicine*, 2011; 30: 1473-1488.
34. Dmitrienko, A, Tamhane, AC. General theory of mixture procedures for gatekeeping. *Biometrical Journal*, 2013; 55: 402-419.
35. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994, 81(3):515-526.



36. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA* 2003; 289(19):2545-53.
37. Gail M., Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985 41:361-372.
38. 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.
39. Dubois MF, Hébert R. Imputation of missing dates of death or institutionalization for time-to-event analyses in the Canadian Study of Health and Aging. *Int Psychogeriatr.* 2001;13 Supp 1:91-7.
40. Lakatos, Edward. Sample sizes based on the log-rank statistic in complex clinical trials. *Biometrics* 1988 44:229-241.
41. J. Shih. Sample size calculation for complex clinical trials with survival. *Controlled Clinical Trials* 1995 16:395-407
42. Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol* 2007 July;6(7):611-9.
43. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; 372:1791-1800.⁹⁹
44. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlio DE, Steg PG, et al. Twelve of 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66.⁹⁹
45. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trial. *Lancet* 2015;385;2371-82.⁹⁹
46. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;Sep 8;365(10):883-91.⁹⁹

⁹⁹ References added as per Amendment 8.



13. Protocol amendments

Protocol version history

Original Protocol Version 1.0 – Approved 19 OCT 2012

Revised Protocol Version 1.1 – Approved 28 NOV 2012

The revised protocol contains some additional clarifications on data collection. The changes to the protocol are not substantial and do not affect the study design, but must be done for consistency with the CRFs.

The word “primary” has been removed when linked to the outcome for the pantoprazole randomization, and similarly a paragraph describing the “primary” outcome for the pantoprazole randomization has been removed from the protocol sections where they are not applicable. Rationale and implications: Although the outcome of the composite of GI bleeding is the “primary” objective of the pantoprazole randomization, it is not part of the primary objective of the trial and, thus, not a primary variable of the trial. Therefore, the word “primary” has been removed. The intent and the analysis plan remains the same.

A consistent use of the terms “outcome” and “variable” has been ensured. While the term “outcome” is used to describe a clinical event to be observed in the trial, e.g. stroke, the term “variable” refers to the statistical variable to be analyzed, e.g. the time to the first occurrence of the outcome since randomization. The wording in section 4.2 has been adapted to consistently reflect this throughout the protocol.

The timing of the study questionnaires have been further clarified in respective protocol sections. Collection of two additional questionnaires (health care costs information and assessment of the driving status) and additional information relative to the CABG surgery for subjects randomized post CABG surgery (EuroSCORE) have been added to the respective study visit section. Collection of two questionnaires (Diet and Activity) has been removed from the Final Follow-up Visit. Collection of blood sampling relevant for COMPASS MIND study has been included in the relevant study visit section.

13.1 Amendment 6

The eligibility criteria for study population of subjects with coronary artery disease (CAD) and peripheral artery disease (PAD) have been simplified and clarified. Despite the improved language and adjustment of the criteria, the target population remains largely unchanged. Additionally, there is an increase in the overall sample size of the study by 1900, from 19,500 to 21,400 randomized subjects, of which 900 will be enrolled in Japan.

There are otherwise other minor changes, and logistical improvements or clarifications throughout the protocol.

13.1.1 Overview changes to the study

The following changes are made to Original Protocol Version 1.1.

Administrative, editorial and typographical corrections were made throughout the document including Table 7-1 and the list of abbreviations. These changes do not affect the overall study concept.

Modification 1: Name of the PPD [redacted] has been updated.

Rationale: PPD [redacted] replaces PPD [redacted] as the PPD [redacted] for the COMPASS study.

Sections affected:

- Title page
- Signature of the sponsor's medically responsible person

Modification 2: Minor clarifications for the secondary and tertiary efficacy outcomes

Rationale: The following sections now contain minor clarifications to address either the terms that were omitted in the previous protocol or to reflect the changes in the associated sections of this protocol amendment. These clarifications are as follows: 1) addition of revascularization to the secondary composite outcomes, and 2) addition of the stent thrombosis and coronary artery bypass graft failure to the tertiary outcomes. These additions do not affect the analysis of the corresponding statistical variables.

Sections affected:

- Synopsis: Study objectives
- Section 2: Study objectives
- Section 7.3 Efficacy
- Section 7.5.3.1 Protocol-specific exceptions to SAE reporting (new section)
- Section 8.3.2 Secondary efficacy outcomes
- Section 8.3.3 Tertiary and other efficacy outcomes

Modification 3: Clarifications in the main criteria for inclusion

Rationale: Originally, the protocol mandated that subjects with PAD under the age of 65 have documented atherosclerosis in at least two vascular beds or at least two additional cardiovascular risk factors. This requirement was based on the general observation that



cardiovascular risk is closely correlated with increasing age. Thus, subjects under the age of 65 with either coronary or peripheral artery disease would have a substantially lower rate of cardiovascular death, myocardial infarction, or stroke than those over the age of 65.

However, further scrutiny of the recent data from the On-Target (1) and Transcend (2) trials demonstrated that event rates in subjects under the age of 65 with PAD are about 50% higher than those with CAD and are well over 4%. This observation prompted the removal of the requirement for two additional risk factors or disease in at least two vascular beds for PAD subjects under the age of 65; such subjects are at high risk even without additional risk factors and will potentially benefit from a more effective rivaroxaban-based treatment.

Based on the questions received from the sites, it became evident that additional clarifications regarding definition of vascular beds were required. The definition is now specified in the protocol amendment.

References:

1. The ONTARGET Investigators. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N Engl J Med* 2008; 358:1547-1559
2. The Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. Published on-line 29 August 2008; 372(9644):1174-83.

Sections affected:

- Synopsis: Diagnosis and Main Criteria for Inclusion
- Section 5.1.1 Inclusion criteria

Modification 4: Minor clarifications for consistency

Minor, consistency and logistical clarifications were made throughout the document. These changes do not affect the overall study concept.

Sections affected:

- Synopsis: Methodology
- List of abbreviations
- Section 1.1 Background
- Section 1.2.1 Rivaroxaban



- Section 1.2.2 Aspirin and anticoagulants
- Section 1.2.3 Proposed rivaroxaban evaluation
- Section 4.1 Design overview
 - Section 4.1.1 Subjects randomized after CABG surgery
- Section 4.3.1 Overall design rationale
- Section 5 Study population
- Section 6.1 Treatments to be administered
 - Section 6.1.1 Run-in
 - Section 6.1.2 Randomization
- Section 6.4.1 Dose modification
 - Section 6.4.2 Dose modification and treatment guidance
 - Section 6.4.2.1 Guidance for the treatment of subjects who require an invasive procedure
 - Section 6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery
 - Section 6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting
- Section 6.6 Drug logistics and accountability
- Section 6.9 Prior and concomitant therapy
 - Section 6.9.2 Clopidogrel (or any other non-study antiplatelet treatment)
 - Section 6.9.4 Proton pump inhibitor treatment
- Section 7.2.3 Other baseline characteristics
- Section 7.3 Efficacy
- Section 8.3.5 Outcome of pantoprazole randomization
- Section 8.3.6 Subgroup variables



- Section 8.4.5 Analysis of the outcome for pantoprazole randomization
- Section 8.4.6 Subgroup Analysis
- Section 14.1 COMPASS MIND Substudy

Modification 5: Clarification about the subjects with the need for the proton pump inhibitor (PPI) treatment

Rationale: The initial protocol required that the subjects with a need for proton pump inhibitor should not be randomized to the PPI. The clarification in this protocol amendment specifies that the need for the PPI refers to subjects who have a continuous need for treatment with the PPI.

Sections affected:

- Synopsis: Methodology
- Section 1.1 Background
- Section 4.1 Design overview
- Section 5.1.2 Exclusion criteria
- Section 6.1.2 Randomization
- Section 6.9.4 Proton pump inhibitor treatment

Modification 6: The number of subjects in the trial has been increased.

Rationale: The number of subjects in the trial has been increased to: ~23,500 enrolled and ~21,400 randomized (10% non-compliance rate is anticipated the run-in period). The reason for increasing the number of subjects is based on emerging data from the ORIGIN trial (1) and the Vorapaxar secondary prevention trial (2), a realistic event rate is 3.5-4% rather than 4-4.5% which mandates an increase in numbers of subjects or duration of follow up to maintain study power.

References:

1. The ORIGIN Trial Investigators. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. N Engl J Med 2012; 367:319-328
2. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012 April 12;366(15):1404-13.



Sections affected:

- Synopsis: Number of subjects
- Section 4.1 Study design
- Section 5 Study population
- Section 8.6 Determination of the sample size

Modification 7: Clarification on one of the referenced studies.

Rationale: Some additional clarification regarding the Voraxapar study (TRA 2 P-TIMI 50) is now included.

Sections affected:

- Section 1.2.2 Aspirin and anticoagulants

Modification 8: Addition of CABG specific objectives

Rationale: In the original protocol, the objectives for the CABG subjects and testing for graft patency were not formally outlined. The protocol amendment now includes these objectives.

Sections affected:

- Section 2 Study Objectives

Modification 9: Clarification on the timing of the administration of the study related questionnaires.

Rationale: Considering the older subjects participating in the COMPASS study, it may be difficult to have all of the study related questionnaires administered at one visit. Therefore, the timing of the administration of the questionnaires now allows some flexibility to when these questionnaires should be completed.

Sections affected:

- Section 4.1 Design overview
- Section 7.1.1 tabulated overview

Modification 10: Changes in the informed consent timing for CABG subjects, and requirement for the angiography at 1 year post surgery for CABG subjects

Rationale: CABG subjects can now sign consent for participation in the evaluation of graft patency either before or after CABG surgery. Irrespective of the timing of consent, the



decision to randomize is based on the information available to the investigator on Day 4 or later post-op. Surgeons will not randomize if information becomes available post-operatively that the treatment is not in the subject's best interests. Moreover, in some centers, it is not feasible to get the consent before surgery because subjects are admitted the evening before surgery. Thus, for some subjects, it may be more appropriate to approach them once they have begun recovering from surgery and are stable and ready to be discharged home or transferred to a rehabilitation center.

Approximately at 1 year post-CABG, certain number of sites routinely perform invasive coronary angiography rather than CT angiography; thus, the protocol amendment now allows the invasive angiography as an acceptable alternative to CT angiography.

Sections affected:

- Section 4.1.1 Subjects randomized after CABG surgery
- Section 7.1.1 tabulated overview
- Section 7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+)

Modification 11: Clarification on the study population and the study investigators qualifications

Rationale: The new paragraph in the protocol amendment summarizes that COMPASS study is enrolling subjects with the high risk of the incident cardiovascular disease. Additionally, based on the request from South American regulatory authority, the investigator qualifications are now further clarified.

Sections affected:

- Section 5 Study population

Modification 12: The section defining eligibility criteria for subjects with coronary artery disease has been modified

Rationale: First, only subjects with a history of previous myocardial infarction (most recent episode) within the past 20 years are eligible, if no other CAD criteria are met. The risk of recurrent event in a subject who has been stable without other complications for more than 20 years is likely to be low, diminishing their potential benefit from a new treatment.

Second, the emphasis of this protocol with respect to coronary artery disease is subjects with multi-vessel disease. With the increasing use of non-invasive means of screening for coronary disease, the potential exists for identification of subjects with positive exercise stress

test to have only single vessel coronary artery disease. Thus, the requirement for stress studies has been further clarified.

Furthermore, with respect to CABG surgery, the protocol previously restricted this to multi-vessel surgery within one week or at least four years prior to randomization (unless the patient had recurrent ischemic events in the first four years after surgery). The recently completed one year follow-up of the CORONARY trial (1) and the five year follow-up of the SYNTAX trial (2) have shown that event rate in subjects with prior CABG surgery is in the order of 3.5-4% per year, even during the first four years after surgery. Thus, these subjects need to be given the opportunity to participate in COMPASS, as they are at substantial risk and could benefit from a new treatment that is potentially more effective than aspirin.

References:

1. Andre Lamy et al. for CORONARY Investigators. Off-Pump or On-Pump Coronary-Artery Bypass Grafting at 30 Days. N Engl J Med 2012; 366:1489-1497
2. Serruys PW et al. for SYNTAX Investigators. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Engl J Med 2009; 360:961-972

Sections affected:

- Section 5 Study population

Modification 13: Section defining the eligibility criteria for subjects with peripheral artery disease has been modified

Rationale: Asymptomatic carotid disease carries a higher risk of MI than stroke on average and carotid endarterectomy (CEA), while reducing the risk of stroke (ARR 0.6% per year) does not alter the cardiac risk. So a previous endarterectomy identifies an individual with an increased cardiac risk. The original observation was made by John Norris (1). Incidentally, the cardiac risk correlates with degree of stenosis and a cutoff of 50% ensures selection of high risk asymptomatic disease.

In the NASCET Trial of surgery for symptomatic carotid stenosis, the rate of MI at 5 years was ~19% (2).

References:

1. Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. N Engl J Med. 1986 Oct 2;315(14):860-5.
2. Ferguson GG et al for The North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. The North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1999; 30: 1751-1758

Sections affected:

- Section 5 Study population

Modification 14: Clarifications in the Exclusion criteria

Rationale: In the section on drug interactions, strong inducers of cytochrome P450 3A4 are now excluded. These were not previously listed in the protocol.

Furthermore, there is an additional clarification on women who are pregnant, breastfeeding, or of childbearing potential.

Participation of subjects who concomitantly participate in another study with an investigational drug, or have contraindication to any study procedure is now excluded.

Additionally, it is now clarified that the subjects who a continuous need for treatment with PPI should not be randomized to pantoprazole arm.

Sections affected:

- Section 5.1.2 Exclusion criteria

Modification 15: Clarifications in the Discontinuations of subjects from study treatment

Rationale: The protocol now clarifies that even the subjects with study outcomes need to be followed at regular study visits until the end of the study. Furthermore, besides collection of survival status information throughout the study, the outcome information is also required in subjects who prematurely terminate the study/study treatment.

Sections affected:

- Section 5.2 Discontinuation of subjects from study treatment

Modification 16: Clarification about the aspirin treatment

Rationale: The protocol amendment clarifies that the aspirin used in the study is enteric coated. Furthermore, the clarification is now included that the terms “aspirin” and “acetyl salicylic acid” are used interchangeably.

Sections affected:

- Section 6.1 Treatments to be administered
- Section 6.2 Identity of study treatment

Modification 17: Clarification on the treatment compliance during run-in

Rationale: The intent of the run in is to optimize subject retention in the study. While the 80% drug adherence during run-in is still required in the protocol, it is recognized that they may be certain circumstances, e.g. outside of subject's control, where the drug adherence may be somewhat affected. Therefore, the target compliance during run-in was amended to "at least 80% except for extenuating circumstances".

Sections affected:

- Section 6.1.2 Randomization
- Section 7.1.2.3 Randomization visit (Day 0 ± 5 days)

Modification 18: Change in the section on treatment guidance with study pantoprazole

Rationale: Compared to the initial protocol, the summary of the treatment guidance with study pantoprazole is now found only in one section. This was done to further simplify the protocol.

Sections affected:

- Section 6.4.2 Dose modifications and treatment guidance
- Section 6.4.2.1 Guidance for the treatment of subjects who require an invasive procedure
- Section 6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery
- Section 6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting
- Section 6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors
- Section 6.9.3 Anticoagulant treatment
- Section 6.9.4 Proton pump inhibitor treatment

Modification 19: Combined CYP 3A4 and p-Glycoprotein Inhibitors and systemic azole antimycotics

Rationale: The title of the relevant protocol sections has been updated to include CYP 3A4 inducers. Also, the concomitant use of strong CYP 3A4 inducers has now been included in the protocol due to the potential for reduction in the rivaroxaban plasma concentrations if used concomitantly. Additionally, macrolide antibiotics are now removed: if used concomitantly with rivaroxaban, their effect on mean rivaroxaban AUC and C_{max} is considered to be clinically not relevant (see rivaroxaban IB and Company Core Data sheet). Furthermore, the



list of systemic antifungal drug provides some examples of the systemic antimycotics that should not be taken concomitantly with rivaroxaban.

Sections affected:

- Section 6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors

Modification 20: Revision of time windows and footnotes under section Tabulated overview

Rationale: Compared to previous protocol, the footnotes under section 7.1.1 Tabulated overview are now revised to reflect the changes in the related protocol sections. Specifically, this section now clarifies the timing of the clinic visits, especially under unforeseen circumstances when the visit time window may be missed. Similarly, the timing for administration of the questionnaires and DNA and blood collection has been further clarified. With this protocol amendment, the target is still to include subjects in the first week following CABG surgery (4-7 days), but randomization is allowed up to Day 14 post-CABG for medical or logistical reasons.

Sections affected:

- Section 7.1.1 Tabulated overview

Modification 21: Minor clarifications in timing of the visit assessments

Rationale: These protocol sections now contain minor editorial revisions/updates: A specification about the administration of the questionnaires for post-CABG subjects has now been included, as well as the allowance for the use of invasive or noninvasive coronary angiography for post-CABG subjects. Furthermore, these sections now include the specification on the timing of blood collection. Namely, at the start of the run-in period, blood samples (for creatinine and cholesterol) up to 1 year old are acceptable to determine the subject's preliminary eligibility. However, at randomization the blood samples should not be older than 3 months.

Sections affected:

- Section 7.1.2.2 Screening and Run-in visit(s)
- Section 7.1.2.3 Randomization visit (Day 0 ± 5 days)
- Section 7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+)

Modification 22: Changes in the efficacy section

Rationale: The paragraph on hospitalization data has been moved from the safety section to efficacy section.



Sections affected:

- Section 7.3 Efficacy
- Section 7.5.3.1 Protocol-specific exceptions to SAE reporting

Modification 23: Changes in the safety section

Rationale: Due to errors in reporting of the study outcomes as e.g. SAEs, the whole safety section has been revised to clarify the requirements for the safety reporting. Namely, few new sections were included to specify 1) the categorization of the AEs, 2) to help with determination of the causal relationship between the study drug and events, and 3) further outline which events are considered as outcomes and should be reported as such. Additionally, few sections have been placed in different order to help clarify the AE reporting requirements. Data Safety Monitoring Board (DSMB) section is now removed, since the details on the DSMB procedures are specified in the respective DSMB charter. Section on pregnancy contains requirement(s) for the reporting of the abnormal pregnancies.

Sections affected:

- Section 7.5.1 Definition of (Serious) Adverse Event
- Section 7.5.2 Causal relationship
- Section 7.5.3.1 Protocol Specific Exemptions to SAE Reporting
- Section 7.5.3.2 Reporting of (S)AEs
- Section 7.5.3.3 Adverse events of special safety interest
- Section 7.5.3.5 Pregnancies
- Section 7.5.3 Data Safety Monitoring Board
- Section 7.5.4 Reporting of events to Bayer by PPD and compliance with regulatory authorities' reporting requirements

Modification 24: Changes in the determination of the sample size

Rationale: Modifications to the event rate assumptions have been inserted, reflecting the change in sample size. Sections affected:

- Section 8.6 Determination of sample size

**Modification 25:** Changes in the Publication policy

Rationale: The clarification that the Operations Committee also serves as Publication Committee is now included.

Sections affected:

- Section 11.3 Publication policy

Modification 26: Reference update

Rationale: Two references have been updated: 1 and 2.

Sections affected:

- Section 12 References

Modification 27: Changes in the MRI sequence and DNA blood collection for the COMPASS MIND

Rationale: This protocol section now clarifies the MRI sequences and the timing of the DNA/blood collections.

Sections affected:

- Section 14.1 COMPASS MIND Substudy



13.1.2 Changes to protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the “old text”. Additions are underlined in the “new text”. Corrections of typing errors or omissions are not highlighted in this amendment.

Title page

This section was changed as a result of Modification 1.

Old Text:

PPD [REDACTED]

~~Bayer Pharma AG
Aprather Weg 18a, Building 402
42113 Wuppertal, Germany
Tel.: PPD [REDACTED]~~

New Text:

PPD [REDACTED]

PPD [REDACTED]

Bayer HealthCare Pharmaceuticals, Inc.
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915
United States
Tel.: PPD [REDACTED]

Signature of the sponsor’s medically responsible person

This section was changed as a result of Modification 1.

Old Text:

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD [redacted]

Role: PPD [redacted]

New Text:

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD [redacted]

Role: PPD [redacted]

Synopsis

This section was changed as a result of Modification 2.

Old Text:

Study objective(s)	<p>Secondary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> 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 (myocardial infarction, stroke, cardiovascular death, and venous thromboembolism) and cardiovascular hospitalization compared with aspirin 100 mg od in subjects with CAD or PAD
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New Text:

Study objective(s)	<p>Secondary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> 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 (myocardial infarction, stroke, cardiovascular death, <u>revascularization</u>, and venous thromboembolism) and cardiovascular hospitalization compared with aspirin 100 mg od in subjects with CAD or PAD
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Synopsis

This section was changed as a result of Modifications 3.

Old Text:

<p>Diagnosis and main criteria for inclusion</p>	<p>Patients are eligible for inclusion if they have coronary artery disease or peripheral artery disease and meet at least one of the following criteria:</p> <ul style="list-style-type: none"> Age ≥65 years
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	<ul style="list-style-type: none"> • Age <65 years with disease in two vascular beds or at least 2 additional cardiovascular risk factors <p>Additional cardiovascular risk factors are:</p> <ul style="list-style-type: none"> • Current smoker • Diabetes mellitus • Renal dysfunction with estimated glomerular filtration rate <60 ml/min • Heart failure • Non-lacunar ischemic stroke ≥1 month ago
--	--

New Text:

<p>Diagnosis and main criteria for inclusion</p>	<p><u>Subjects</u> are eligible for inclusion if they:</p> <ul style="list-style-type: none"> • <u>Meet criteria for CAD* and/or PAD</u> <p><u>*Subjects with CAD must also meet at least one of the following criteria:</u></p> <ul style="list-style-type: none"> • Age ≥65 years, <u>or</u> • Age <65 years <u>and documented atherosclerosis or revascularization involving at least 2 vascular beds[§], or at least 2 additional cardiovascular risk factors:</u> <ol style="list-style-type: none"> 1) Current smoker (<u>within 1 year of randomization</u>) 2) Diabetes mellitus 3) Renal dysfunction with estimated glomerular filtration rate <60 ml/min 4) Heart failure 5) Non-lacunar ischemic stroke ≥1 month ago <p><u>§ Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g. the aorta and arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, or kidneys.</u></p>
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Synopsis

This section was changed as a result of Modifications 4 and 5.

Old Text:

<p>Methodology</p>	<p>The study will comprise 4 periods: screening, run-in, follow-up, and washout. During the screening period, informed consent will be obtained and evaluations of subject eligibility will be performed. The run-in period will occur during the 30 days prior to initiation of study treatment, with the exception of subjects randomized after coronary artery bypass surgery who will not require a run-in. During run-in, subjects will discontinue any current anticoagulant therapy and will begin rivaroxaban placebo and 100 mg aspirin. Treatment of subjects who comply with the run-in treatment and who remain</p>
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	<p>committed to the study, as well as those who are randomized after coronary artery bypass graft surgery will begin on Day 0, which will also signal the initiation of the follow-up period.</p> <p>...</p> <p>*Subjects already taking 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)</p>
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New Text:

Methodology	<p>The study will comprise 4 periods: screening, run-in, follow-up, and washout.</p> <p>During the screening period, informed consent will be obtained and evaluations of subject eligibility will be performed. The run-in period will occur during the <u>28</u> days prior to initiation of study treatment, with the exception of subjects randomized <u>Day 4-7</u> after coronary artery bypass surgery who will not require a run-in. During run-in, subjects will discontinue any current anticoagulant therapy and will begin rivaroxaban placebo and 100 mg aspirin. Treatment of subjects who comply with the run-in treatment and who remain committed to the study, as well as those who are randomized <u>Day 4-7</u> after coronary artery bypass graft surgery will begin on Day 0, which will also signal the initiation of the follow-up period.</p> <p>...</p> <p>*Subjects <u>who have a continuous need for use of</u> 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)</p>
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Synopsis

This section was changed as a result of Modification 6.

Old Text:

Number of subjects	<p>Enrolled = 24,500; randomized = 19500 in approximately 25 to 30 countries worldwide</p> <p>Approximately 24,500 subjects will be enrolled; 19500 will be admitted to the run-in period and 2000 subjects will undergo coronary artery bypass graft but no run-in. A non-compliance rate of 10% is anticipated for those subjects in the run-in period; thus, approximately 19,500 subjects will be randomized (approximately 17,500 subjects who completed run-in and 2000 who underwent coronary artery bypass graft without run-in) in approximately 25 to 30 countries worldwide.</p>
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New Text:

Number of subjects	<p>Enrolled = <u>approximately 23,500</u>; randomized = <u>21,400</u> in approximately 30 countries worldwide</p> <p>Approximately <u>23,500</u> subjects will be enrolled; <u>21,500</u> will be admitted to the run-in period and 2000 subjects will undergo coronary artery bypass graft but</p>
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no run-in. A non-compliance rate of 10% is anticipated for those subjects in the run-in period; thus, approximately 21,400 subjects will be randomized (approximately 19,400 subjects who completed run-in and 2000 who underwent coronary artery bypass graft without run-in) in approximately 30 countries worldwide.

List of abbreviations

This section was changed as a result of Modification 4.

Old Text:

~~ECG~~ ~~Electrocardiogram~~
~~SAS~~ ~~Statistical Analysis Software~~

New Text:

bpm Beats per minute
CAD Coronary artery disease
cm Centimeter
CV Cardiovascular
GPV Global Pharmacovigilance
in Inch
IT Information technology
lb Pound
mmHg Millimeter of mercury
SAS Statistical Analysis System
USA United States of America

Section 1.1 Background

This section was changed as a result of Modifications 4 and 5.

Old Text:

Aspirin, statins and angiotensin converting enzyme (ACE) inhibitors are effective and widely used for the prevention of cardiovascular events in patients with ~~coronary~~ and PAD but the risk of vascular events remains high despite these treatments...

... 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 ~~coronary~~ or PAD ~~who are not treated with dual antiplatelet therapy~~.

...



The trial described herein, 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 ~~coronary~~ or PAD who are receiving ~~standard prevention therapies~~. In the (partial factorial) randomization, patients randomized to receive rivaroxaban in combination with aspirin, rivaroxaban alone or aspirin alone and who do not have a 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

New Text:

Aspirin, statins and angiotensin converting enzyme (ACE) inhibitors are effective and widely used for the prevention of cardiovascular events in patients with CAD and PAD but the risk of vascular events remains high despite these treatments.

...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.

The trial described herein, 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 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 usual care. In the (partial factorial) randomization, patients who do not have a continuous need for use of a proton pump inhibitor will be randomized to receive pantoprazole 40 mg od or placebo for the prevention of major upper gastrointestinal complications, and then randomized to receive rivaroxaban in combination with aspirin, rivaroxaban alone or aspirin alone.

Section 1.2.1 Rivaroxaban

This section was changed as a result of Modification 4.

Old Text:

Rivaroxaban has been tested in randomized controlled trials involving more than ~~60,000~~ patients and has been used by millions of patients worldwide.

New Text:

Rivaroxaban has been tested in randomized controlled trials involving more than 70,000 patients and has been used by millions of patients worldwide.



Section 1.2.2 Aspirin and anticoagulants

This section was changed as a result of Modifications 4 and 7.

Old Text:

Other studies have investigated the potential benefits of combined antiplatelet therapy for long-term prevention of cardiovascular disease. The TRA 2 P-TIMI 50 study demonstrated that the ~~combination of the platelet thrombin receptor antagonist, vorapaxar, and aspirin compared with aspirin alone and continued for 3 years~~ reduced the risk of myocardial infarction, stroke or cardiovascular death by 13% in patients with a history of myocardial infarction, ischemic stroke or PAD but at the cost of an increase in major and intracranial bleeding ~~and with no reduction in cardiovascular mortality~~.

...

~~Preliminary~~ evidence for the efficacy and safety of oral factor Xa inhibitors for the prevention of major cardiovascular events comes from the recently completed AVERROES trial which demonstrated that the oral factor Xa inhibitor, apixaban, compared with aspirin not only reduced the risk of stroke but was also associated with numerically fewer myocardial infarctions with no significant increase in major bleeding.

New Text:

Other studies have investigated the potential benefits of combined antiplatelet therapy for long-term prevention of cardiovascular disease. The TRA 2 P-TIMI 50 study demonstrated that the platelet protease-activated receptor 1 antagonist, vorapaxar added to standard therapy that included aspirin and clopidogrel, compared with standard therapy alone reduced the risk of myocardial infarction, stroke, or cardiovascular death by 13% at 3 years in patients with a history of myocardial infarction, ischemic stroke, or PAD, but at the cost of an increase in major and intracranial bleeding.¹⁸

...

Additional evidence for the efficacy and safety of oral factor Xa inhibitors for the prevention of major cardiovascular events comes from the recently completed AVERROES trial which demonstrated that the oral factor Xa inhibitor, apixaban, compared with aspirin not only reduced the risk of stroke but was also associated with numerically fewer myocardial infarctions with no significant increase in major bleeding.²²



Section 1.2.3 Proposed rivaroxaban evaluation

This section was changed as a result of Modification 4.

Old Text:

... We hypothesize 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 increase in bleeding.

New Text:

... We hypothesize 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 increase in bleeding.

Section 2 Study objectives

This section was changed as a result of Modification 8.

Old Text:

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 (myocardial infarction, stroke, cardiovascular death, and venous thromboembolism) and cardiovascular hospitalization compared with aspirin 100 mg od in subjects with CAD or PAD

New Text:

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 (myocardial infarction, stroke, cardiovascular death, revascularization, and venous thromboembolism) and cardiovascular hospitalization compared with aspirin 100 mg od in subjects with CAD or PAD

...

Objectives for Day 4-7 post-CABG 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 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

Section 4.1 Design overview

This section was changed as a result of Modifications 4, 5, 6 and 9.

Old Text:

This Phase 3, event-driven (at least 2,200 primary efficacy outcome events), randomized controlled trial will have a 3 x 2 partial factorial design and will randomize at least ~~19,500~~ subjects who will receive treatment for an expected average duration of 3 to 4 years. The COMPASS trial will involve 4 periods: screening, run-in, follow-up, and washout.

Prescreening procedures may require informed consent in some countries. In all other study sites, informed consent will be obtained prior to the initiation of any screening procedures. 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.

The run-in period will occur during the ~~30~~ 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 (Section 4.1.1). During run-in, subjects will discontinue any ~~non-study anticoagulant and non-study aspirin~~ therapy and will begin study rivaroxaban placebo and study aspirin 100 mg.

Subjects who successfully complete the run-in period and 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 0, which will also signal the initiation of the follow-up period. Subjects without ~~an ongoing~~ need for treatment with a proton pump inhibitor will be randomized 1:1 to the pantoprazole or pantoprazole placebo and all subjects (including those subjects who entered the study while already receiving a proton pump inhibitor) will then be randomized 1:1:1 to rivaroxaban alone, the combination of rivaroxaban and aspirin or aspirin alone, and their matching placebos as shown in Table 4-1:

Table 4-1. Randomized study treatments*

Study Arm	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 ~~already taking~~ 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)



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 treatment adherence, treatment interruption, outcomes, and adverse events (AEs). Validated questionnaires will be administered at randomization and at Month 24 to collect data on subject health and quality of life (Standard Assessment of Global-Activities in the Elderly [SAGE], Montreal Cognitive Assessment [MoCA], DSS [Digital Symbol Substitution], European Quality of Life-5 Dimensions [EQ-5D], The Interheart Diet Questionnaire, and The International Physical Activity Questionnaire).

New Text:

This Phase 3, event-driven (at least 2,200 primary efficacy outcome events), randomized controlled trial will have a 3 x 2 partial factorial design and will randomize at least 21,400 subjects who will receive treatment for an expected average duration of 3 to 4 years. The COMPASS trial will involve 4 periods: screening, run-in, follow-up, and washout.

Prescreening procedures may require informed consent in some countries. In all other study sites, informed consent will be obtained prior to the initiation of any screening procedures (Section 7.1.2.1). Screening will be performed to determine subject eligibility and will include the review of inclusion and exclusion criteria, physical measurements, laboratory evaluations, etc. (Section 7.1.2.2).

The run-in period will occur during the 28 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 (Section 4.1.1). During run-in, subjects will discontinue any antithrombotic therapy and will begin study rivaroxaban placebo and study aspirin 100 mg.

Subjects who successfully complete the run-in period and 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 0, which will also signal the initiation of the follow-up period. Subjects without a continuous need for treatment with a proton pump inhibitor will be randomized 1:1 to the pantoprazole or pantoprazole placebo and all subjects (including those subjects who entered the study while already receiving a proton pump inhibitor) will then be randomized 1:1:1 to rivaroxaban alone, the combination of rivaroxaban and aspirin or aspirin alone, and their matching placebos as shown in Table 4-1:

Table 4-1. Randomized study treatments*

Study Arm	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)

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 treatment adherence, treatment interruption, outcomes, and adverse events (AEs). Validated questionnaires will be administered before or at the time of randomization, or as soon as possible thereafter, and at Month 24 to collect data on subject health and quality of life (Standard Assessment of Global-Activities in the Elderly [SAGE], Montreal Cognitive Assessment [MoCA], DSS [Digital Symbol Substitution], European Quality of Life-5 Dimensions [EQ-5D], The Interheart Diet Questionnaire, and The International Physical Activity Questionnaire).

Section 4.1.1 Subjects randomized after CABG surgery

This section was changed as a result of Modification 4 and 10.

Old Text:

~~Subjects randomized after CABG surgery will undergo the same screening, follow-up and washout periods as other COMPASS trial subjects but will not undergo a run-in period. The majority of these subjects are expected to undergo screening during the 2-3 weeks before surgery. Subjects randomized post CABG will sign consent prior to surgery and those who survive and remain eligible will undergo randomization between Days 4-7 after surgery, at least 24 hours following the removal of chest tubes and at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis).~~

Subjects randomized after CABG surgery will undergo computed tomography (CT) angiography at 1 year as part of the study protocol unless they have a specific contraindication for CT angiography (e.g., contrast allergy, estimated glomerular filtration rate <30 ml/min).

New Text:

Subjects randomized Day 4-7 after CABG surgery will undergo the same screening, follow-up, and washout as other COMPASS trial subjects but not run-in. Subjects are to sign informed consent before or after the surgery. Randomization will occur between Day 4-7



after surgery, at least 24 hours following the removal of chest tubes and at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis) (Section 7.1.1 Tabulated overview).

Subjects randomized Day 4-7 after CABG surgery will undergo computed tomography (CT) angiography at 1 year as part of the study protocol to assess graft patency unless they have a specific contraindication for CT angiography (e.g., contrast allergy, estimated glomerular filtration rate <30 ml/min). In the event the subject undergoes an invasive coronary angiography at 1 year post CABG for any reason, a CT angiogram may not be required.

Section 4.3.1 Overall design rationale

This section was changed as a result of Modification 4.

Old Text:

The benefit of ~~increasing the~~ intensity of antithrombotic therapy for the prevention of recurrent thrombotic cardiovascular events by adding a second agent to aspirin has been established in trials of dual antiplatelet therapy after an acute coronary syndrome when compared with aspirin alone.

...

To date, no trials have directly compared a new anticoagulant with aspirin for long-term secondary prevention of cardiovascular disease. Prior efforts to identify more effective antithrombotic treatments than aspirin have focused on new antiplatelet therapies (terutroban, a platelet thromboxane receptor antagonist; clopidogrel, prasugrel and ticagrelor, ~~adenosine diphosphate (ADP) receptor~~ antagonists; and vorapaxar, a PAR-1 receptor antagonist) and warfarin.

New Text:

The benefit of increased intensity of antithrombotic therapy for the prevention of recurrent thrombotic cardiovascular events by adding a second agent to aspirin has been established in trials of dual antiplatelet therapy after an acute coronary syndrome when compared with aspirin alone.

...

To date, no trials have directly compared a new anticoagulant with aspirin for long-term secondary prevention of cardiovascular disease. Prior efforts to identify more effective antithrombotic treatments than aspirin have focused on new antiplatelet therapies (terutroban, a platelet thromboxane receptor antagonist; clopidogrel, prasugrel and ticagrelor, P2Y12 antagonists; and vorapaxar, a PAR-1 receptor antagonist) and warfarin.

Section 5 Study population

This section was changed as a result of Modifications 4, 6, 11, 12 and 13.

**Old Text:**

Approximately ~~19,500~~ eligible subjects will be admitted to the run-in period and an additional 2000 will be enrolled post CABG and without run-in. Approximately 10% of run-in subjects are expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study will randomize approximately ~~19,500~~ men and women with objectively confirmed CAD or PAD from ~~25 to~~ 30 countries worldwide.

For the ~~purposes of this trial, the definition of CAD is:~~

- Previous myocardial infarction, or
- ~~Stable angina or unstable angina with documented multi-vessel CAD, > 50% stenosis in at least 2 major coronary arteries on coronary angiography, or positive stress test (electrocardiogram (ECG) or nuclear perfusion scintogram), or~~
- Multi-vessel percutaneous coronary intervention (PCI), or
- Multi-vessel CABG surgery within 1 week or at least 4 years ago or with recurrent angina or ischemia at any time following surgery.[†]

~~† Rationale: The risk of thrombotic events and graft failure increases during the first year post CABG.¹² Following a relatively stable period with low event rates between Year 1 and 4, the risk starts to rise again.²⁸~~

For the ~~purposes of this trial, the definition of PAD is:~~

- Previous aorto-femoral bypass surgery, limb bypass surgery or percutaneous transluminal angioplasty of the iliac or infrainguinal arteries, or
- Previous limb or foot amputation for arterial vascular disease (i.e., excludes trauma), or
- History of intermittent claudication and either an ankle/arm blood pressure (BP) ratio ≤ 0.90 or significant peripheral artery stenosis ($\geq 50\%$) documented by angiography or ~~non-invasive testing~~ by duplex ultrasound, or
- Asymptomatic (i.e., no ipsilateral stroke or transient ischemic attack within 6 months) carotid artery stenosis $\geq 50\%$ as diagnosed by duplex ultrasound or angiography.

New Text:

Approximately 23,500 eligible subjects will be admitted to the run-in period and an additional 2000 will be enrolled post CABG and without run-in. Approximately 10% of run-in subjects are expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study will randomize approximately 21,400 men and women with objectively confirmed CAD or PAD from approximately 30 countries worldwide.



Subjects with high risk of incident cardiovascular disease will be enrolled in the study. Subjects will be treated with rivaroxaban, the combination of rivaroxaban and aspirin, or aspirin on top of usual care. Investigators in the study are selected based on their qualifications and ability to enroll and treat these subjects in accordance with the protocol and applicable standard of care.

For the purpose of determining eligibility for this trial, subjects meeting criteria for CAD must have one or more of the following:

- Myocardial infarction within the last 20 years, or
- Multi-vessel coronary disease* with symptoms or history of stable or unstable angina, or
- Multi-vessel percutaneous coronary intervention (PCI), or
- Multi-vessel CABG surgery

*Refers to stenosis of greater than or equal to 50% in two or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g. exercise or pharmacologic) suggestive of significant ischemia in 2 or more coronary territories; or in 1 coronary territory if at least one other territory has been revascularized

For the purpose of determining eligibility for this trial, subjects meeting criteria for PAD must have one or more of the following:

- Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infrainguinal arteries, or
- Previous limb or foot amputation for arterial vascular disease (i.e., excludes trauma), or
- History of intermittent claudication and one or more of the following: 1) an ankle/arm blood pressure (BP) ratio ≤ 0.90 , or 2) significant peripheral artery stenosis ($\geq 50\%$) documented by angiography, or by duplex ultrasound, or
- Previous carotid revascularization (e.g., endarterectomy, stenting) or asymptomatic (i.e., no ipsilateral stroke or transient ischemic attack within 6 months) carotid artery stenosis $\geq 50\%$ as diagnosed by duplex ultrasound or angiography.



Section 5.1.1 Inclusion criteria

This section was changed as a result of Modification 3.

Old Text:

- CAD or PAD ~~plus~~ at least one of the following:
 - Age ≥ 65
 - Age < 65 ~~plus~~ documented atherosclerosis ~~in~~ two vascular beds or at least two additional risk factors

~~Additional risk factors are:~~

- Current smoker
- Diabetes mellitus
- Renal dysfunction with estimated glomerular filtration rate < 60 ml/min
- Heart failure
- Non-lacunar ischemic stroke ≥ 1 month ago

New Text:

- Meet criteria for CAD* and/or PAD

*Subjects with CAD must also meet at least one of the following criteria:

- Age ≥ 65 , or
- Age < 65 and documented atherosclerosis or revascularization involving at least 2 vascular beds[§], or at least 2 additional risk factors:
 - 1) Current smoker (within 1 year of randomization)
 - 2) Diabetes mellitus
 - 3) Renal dysfunction with estimated glomerular filtration rate < 60 ml/min
 - 4) Heart failure
 - 5) Non-lacunar ischemic stroke ≥ 1 month ago

§ Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g. the aorta and arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, or kidneys.



Section 5.1.2 Exclusion criteria

This section was changed as a result of Modification 5 and 14.

Old Text:

- History of hypersensitivity or known contraindication for rivaroxaban, aspirin, or pantoprazole
- Systemic treatment with strong CYP 3A4 and p-glycoprotein (P-gp) inhibitors (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir)
- Any known hepatic disease associated with coagulopathy
- ~~Female subjects, premenopausal who are not surgically sterile, or, if sexually active not practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and, for those of childbearing potential, who have a positive pregnancy test at screening~~
- Previous assignment to treatment during this study

An additional exclusion for the pantoprazole randomization is:

- Need for treatment with a proton pump inhibitor

New Text:

- History of hypersensitivity or known contraindication for rivaroxaban, aspirin, pantoprazole, or excipients, if applicable.
- Systemic treatment with strong inhibitors of both CYP 3A4 and p-glycoprotein (P-gp) (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine
- Any known hepatic disease associated with coagulopathy
- Subjects who are pregnant, breastfeeding or are of childbearing potential, and sexually active and not practicing an effective method of birth control (e.g. surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization)
- Previous assignment to treatment during this study



- Concomitant participation in another study with investigational drug
- Known contraindication to any study related procedures

An additional exclusion for the pantoprazole randomization is:

- Need for continuous treatment with a proton pump inhibitor

Section 5.2 Discontinuation of subjects from study treatment

This section was changed as a result of Modification 15.

Old Text:

...In all cases, every effort must be made to continue to follow the subject ~~and~~ survival status information must be determined for all subjects ~~at the end of the study.~~

New Text:

...In all cases, including the subjects with the study outcome, every effort must be made to continue to follow the subject at regular study visits. Additionally, survival status and outcome information must be determined for all subjects.

Section 6.1 Treatments to be administered

This section was changed as a result of Modifications 4 and 16.

Old Text:

The study drugs to be administered in this trial include the antithrombotic drugs, rivaroxaban and aspirin; the proton pump inhibitor pantoprazole; and their matching placebos.

New Text:

The study drugs to be administered in this trial include the antithrombotic drugs, rivaroxaban and enteric-coated aspirin; the proton pump inhibitor pantoprazole; and their matching placebos.

Section 6.1.1 Run-in

This section was changed as a result of Modification 4.

Old Text:

During the run-in period, Day ~~-30~~ to Day -1 (~~≠ 5 days~~), eligible subjects (excluding those who are randomized ~~during the first week~~ after CABG surgery) who have signed informed consent and stopped non-study anticoagulants and aspirin will receive rivaroxaban placebo bid and aspirin 100 mg od.

New Text:

During the run-in period, Day -28 to Day -1, eligible subjects (excluding those who are randomized Day 4-7 after CABG surgery) who have signed informed consent and stopped non-study anticoagulants and aspirin will receive rivaroxaban placebo bid and aspirin 100 mg od.

Section 6.1.2 Randomization

This section was changed as a result of Modifications 4, 5 and 17.

Old Text:

Subjects who have completed the run-in period with at least 80% adherence to treatment with rivaroxaban placebo bid and aspirin 100 mg od and who wish to continue in the study, and those who are being randomized ~~during the first week~~ after CABG surgery and who do not have a need to take a proton pump inhibitor, will initially be randomized 1:1 to receive pantoprazole 40 mg od or matching placebo od, stratified by center.

New Text:

Subjects who have completed the run-in period with adherence to treatment with rivaroxaban placebo bid and aspirin 100 mg od of at least 80% except for extenuating circumstances, and who wish to continue in the study will be randomized. Subjects being randomized after run-in



and those who are being randomized Day 4-7 after CABG surgery (Section 7.1.1 Tabulated overview) and who do not have a continuous need to take a proton pump inhibitor, will initially be randomized 1:1 to receive pantoprazole 40 mg od or matching placebo od, stratified by center.

Section 6.2 Identity of study treatment

This section was changed as a result of Modification 16.

Old Text:

...Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

New Text:

...Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request. For the purpose of this study, the term "aspirin" is used interchangeably with the term "acetyl salicylic acid".

Section 6.4.1 Dose modifications

This section was changed as a result of Modification 4.

Old Text:

Permanent study drug ~~interruption~~ should be recorded on the corresponding follow-up case report form, giving the date and primary reason for stopping the study drug. If one of the study treatments needs to be interrupted, other study treatments must be continued.

New Text:

Permanent study drug interruption should be recorded on the corresponding follow-up case report form, giving the date and primary reason for stopping the study drug. If one of the study treatments needs to be discontinued, other study treatments must be continued.

Section 6.4.2 Dose modifications and treatment guidance

This section was changed as a result of Modifications 4 and 18.

Old Text:

This section provides a general guide for investigators on the management of subjects who develop intercurrent illnesses or bleeding during the course of the COMPASS trial. The guidance provided in this section does not replace clinical judgment in determining the appropriate management strategy for individual subjects.

New Text:

This section provides a general guide for investigators on the management of subjects who develop intercurrent illnesses or bleeding during the course of the COMPASS trial. The guidance provided in this section does not replace clinical judgment nor usual care in determining the appropriate management strategy for individual subjects. For specific treatment guidance with study pantoprazole/pantoprazole placebo see Section 6.9.4

Section 6.4.2.1 Guidance for the treatment of subjects who require an invasive procedure

This section was changed as a result of Modifications 4 and 18.

Old Text:

~~...If study aspirin/aspirin placebo is interrupted, non-study aspirin may be used. Study pantoprazole/pantoprazole placebo should not be interrupted unless subjects develop a need for treatment with a proton pump inhibitor.~~

New Text:

...If study aspirin/aspirin placebo is interrupted, non-study aspirin may be used.

Section 6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery

This section was changed as a result of Modifications 4 and 18.

Old Text:

~~Subjects who are scheduled to be randomized during the first week after CABG surgery will not participate in the run-in phase but will sign informed consent and undergo screening before the surgery (Section 4.1.1). The timing of randomization should be no earlier than 4~~



~~days and no more than 7 days after surgery and only once the chest tubes are removed and hemostasis is secure.~~

...

In all cases, the goal should be to resume study antithrombotic drugs within 7 days and prior to being discharged from hospital.

~~Study pantoprazole/pantoprazole placebo should not be interrupted unless subjects develop a need for treatment with a proton pump inhibitor.~~

New Text:

Subjects who are scheduled to be randomized Day 4-7 after CABG surgery will not participate in the run-in phase (Section 4.1.1). Randomization should only be performed between Day 4-7 post-CABG and at least 24 hours following the removal of chest tubes and at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis).

In all cases, the goal should be to resume study antithrombotic drugs within 14 days and prior to being discharged from hospital.

Section 6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting

This section was changed as a result of Modifications 4 and 18.

Old Text:

...Standard anticoagulant therapy can be used without regard to the timing of the most recent dose of study rivaroxaban/rivaroxaban placebo because the doses of rivaroxaban being tested in the COMPASS trial are lower than the 20 mg dose given for stroke prevention in atrial fibrillation and the half-life is short, 5-13 hours.

~~Study pantoprazole/pantoprazole placebo should not be interrupted unless subjects have developed a need for treatment with a proton pump inhibitor.~~

New Text:

...Standard anticoagulant therapy can be used without regard to the timing of the most recent dose of study rivaroxaban/rivaroxaban placebo because the doses of rivaroxaban being tested in the COMPASS trial are lower than the 15 or 20 mg dose given for stroke prevention in atrial fibrillation and the half-life is short, 5-13 hours.



Section 6.6 Drug logistics and accountability

This section was changed as a result of Modification 4.

Old Text:

... The responsible site personnel will confirm the date ~~and time~~ of receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. .

New Text:

...The responsible site personnel will confirm the date of receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol.

Section 6.9 Prior concomitant therapy

This section was changed as a result of Modification 4.

Old Text:

As described in Section 5.1.2, Exclusion Criteria, the use of the following agents is not permitted at study entry: systemic treatment with strong CYP 3A4 and P-gp ~~inhibitors~~ (e.g., systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir). Additionally, subjects with a need for dual antiplatelet therapy or oral anticoagulant therapy are not eligible for inclusion in COMPASS.

New Text:

As described in Section 5.1.2, Exclusion Criteria, the use of the following agents is not permitted at study entry: systemic treatment with strong inducers of CYP 3A4 (e.g. rifampicin) and inhibitors of both CYP 3A4 and P-gp (e.g., systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir). Additionally, subjects with a need for dual antiplatelet therapy or oral anticoagulant therapy are not eligible for inclusion in COMPASS.

Section 6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors

This section was changed as a result of Modifications 18 and 19.

Old Text:

6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors

Strong inhibitors of both CYP 3A4 and p-glycoprotein increase plasma concentrations of rivaroxaban and are contraindicated in subjects taking rivaroxaban. These include systemic azole antifungal drugs (ketoconazole), ~~macrolide antibiotics (erythromycin, azithromycin, clarithromycin)~~ and HIV protease inhibitors. If any of these treatments are needed,

randomized study rivaroxaban/rivaroxaban placebo and aspirin/aspirin placebo must be temporarily discontinued and open-label aspirin should be begun. ~~Study pantoprazole/pantoprazole placebo should not be interrupted unless subjects develop a need for treatment with a proton pump inhibitor.~~

New Text:

6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors and CYP 3A4 inducers

Strong inhibitors of both CYP 3A4 and p-glycoprotein increase plasma concentrations of rivaroxaban and are contraindicated in subjects taking rivaroxaban. These include systemic azole antifungal drugs (e.g. ketoconazole, itraconazole, posaconazole, etc.), and HIV protease inhibitors. Additionally, strong inducers of CYP 3A4 such as, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine can reduce the plasma concentrations of rivaroxaban. If any of these treatments are needed, randomized study rivaroxaban/rivaroxaban placebo and aspirin/aspirin placebo must be temporarily discontinued and open-label aspirin should be begun.

Section 6.9.2 Clopidogrel (or any other non-study antiplatelet treatment)

This section was changed as a result of Modification 4.

Old Text:

Subjects who develop a need for treatment with non-study antiplatelet therapy, such as aspirin plus clopidogrel (e.g., subjects who experience an acute coronary syndrome, those who undergo percutaneous coronary intervention with stent insertion) must ~~discontinue~~ study rivaroxaban/rivaroxaban placebo. Study rivaroxaban/rivaroxaban placebo must be restarted once dual antiplatelet therapy is stopped (i.e., after completion of an adequate duration of dual antiplatelet treatment). Additional guidance is provided in Section 6.4.2.3.

New Text:

Subjects who develop a need for treatment with non-study dual antiplatelet therapy, such as aspirin plus clopidogrel (e.g., subjects who experience an acute coronary syndrome, those who undergo percutaneous coronary intervention with stent insertion) must interrupt study treatment of rivaroxaban/rivaroxaban placebo. Study rivaroxaban/rivaroxaban placebo must be restarted once dual antiplatelet therapy is stopped (i.e., after completion of an adequate duration of dual antiplatelet treatment). Additional guidance is provided in Section 6.4.2.3.

Section 6.9.3 Anticoagulant treatment

This section was changed as a result of Modification 18.

Old Text:

...In subjects who develop a need for anticoagulant therapy, study aspirin/aspirin placebo may also be interrupted, at the discretion of the investigator. ~~Study pantoprazole/pantoprazole~~



~~placebo should not be interrupted unless subjects have a need for treatment with a proton pump inhibitor.~~

New Text:

...In subjects who develop a need for anticoagulant therapy, study aspirin/aspirin placebo may also be interrupted, at the discretion of the investigator.

Section 6.9.4 Proton pump inhibitor treatment

This section was changed as a result of Modifications 4 and 18.

Old Text:

Subjects who develop a need for treatment with a proton pump inhibitor (e.g., gastroduodenal ulcer) should discontinue study pantoprazole/pantoprazole placebo while receiving non-study proton pump inhibitor treatment. Study pantoprazole/pantoprazole placebo ~~must~~ be restarted in all subjects who no longer have a need for proton pump inhibitor therapy.

New Text:

Subjects who develop a continuous need for treatment with a proton pump inhibitor during the study (e.g., gastroduodenal ulcer) should discontinue study pantoprazole/pantoprazole placebo while receiving non-study proton pump inhibitor treatment. Study pantoprazole/pantoprazole placebo should be restarted in all subjects who no longer have a continuous need for proton pump inhibitor therapy.

Section 7.1.1 Tabulated overview

This section was changed as a result of Modification 20.

Old Text:

	Pre-Screening ^a	Screening/Run-in	Randomization	Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Washout
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m
Windows			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d
Health Care Costs			X															
Driving Status			X															
EuroSCORE for subjects randomized post CABG surgery			X															
CT coronary angiography ^h								X ^h										
MRI brain ⁱ			X														X	
Outcomes				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
Study drug dispensed		X ^k	X ^l			X		X	X	X	X	X	X	X	X	X		
Study drug adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug accountability			X	X		X		X	X	X	X	X	X	X	X	X	X	

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

- Pre-screening visit is not mandatory and will be conducted only in some centers and for some subjects. Subjects who will be randomized during the first week after CABG surgery do not require pre-screening.
- Weight, height, waist and hip circumference, heart rate, ankle-brachial blood pressure index
- Serum creatinine, total cholesterol

- d. If not available within prior ~~3 months~~
- e. Repeat serum creatinine in patients being enrolled post CABG surgery
- f. Blood & DNA collection at randomization and ~~blood collection at 1 month for central evaluation will be collected in subjects participating in the COMPASS-MIND substudy~~
- g. Using the European Quality of Life-5 Dimensions questionnaire and to be performed at randomization, 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 in all subjects who are randomized ~~during the first week~~ after CABG (except in subjects those with specific contraindications)
- i. MRI of the brain will be performed only in COMPASS-MIND substudy subjects, at the time of randomization (or soon thereafter) and ~~at~~ 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. Dispense run-in medications. CABG surgery patients will be randomized ~~during the first week~~ 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

Visit	Pre-Screening ^a	Screening/Run-in	Randomization ²	Follow-up														Washout
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Wash out
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m
Windows ^a			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d
EuroSCORE for subjects randomized post CABG surgery			X															
CT coronary angiography ^h								X ^h										
MRI brain ⁱ			X														X	
Outcomes			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
Study drug dispensed		X ^k	X ^l			X		X	X	X	X	X	X	X	X	X		
Study drug adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug accountability			X	X		X		X	X	X	X	X	X	X	X	X	X	

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

- 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.
- Weight, height, waist and hip circumference, heart rate, ankle-brachial blood pressure index
- Serum creatinine, total cholesterol
- If not available within 1 year prior.
- 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.
- 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 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 randomization, 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 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 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, at the time of randomization (or soon thereafter, within 3 months) 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.



Section 7.1.2.2 Screening and Run-in visit(s)

This section was changed as a result of Modification 21.

Old Text:

The aim of the screening visit is to confirm ~~eligibility and perform baseline laboratory assessments and in most subjects will be performed on the day of the run-in visit as long as laboratory tests have been performed within 3 months and a negative pregnancy test result is available for premenopausal subjects.~~ For subjects who are randomized ~~during the first week~~ after CABG surgery the screening visit ~~will~~ be performed prior to surgery (Section 4.1.1). ~~The Screening/Run-in Visit will occur 4 weeks prior to randomization; however, screening may be earlier if performed on a separate day.~~ Screening/run-in activities include:

...

- 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
- ~~Collect blood for local laboratory assessment of creatinine and total cholesterol (if not performed at pre-screening/screening/run-in, or previous laboratory assessments were conducted > 3 months prior)~~
- ~~Collect blood for local laboratory assessment of creatinine and total cholesterol (previous laboratory assessments were conducted > 3 months prior)~~

...

- Obtain medication code for run-in study treatment and dispense run-in study medications (not applicable for subjects who are randomized ~~during the first week~~ after CABG surgery)

New Text:

The aim of the screening visit is to confirm eligibility. Laboratory results of creatinine and total cholesterol performed within a year of this visit can be used to assess eligibility. Otherwise, obtain relevant laboratory tests. For subjects who are randomized Day 4-7 after CABG surgery, the screening visit may be performed prior to or after surgery (Section 4.1.1). Screening/run-in activities include:

...

- 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. (In patients randomized Day 4-7 post CABG, the questionnaires should be performed at the 1 month visit).

...



- Obtain medication code for run-in study treatment and dispense run-in study medications (not applicable for subjects who are randomized Day 4-7 after CABG surgery)

A subject can be re-screened/re-run-in, if not previously randomized to study treatment:

- Obtain written informed consent, if applicable
- Repeat/complete the rest of the screening/run-in activities, where applicable.

Section 7.1.2.3 Randomization visit (Day 0 ± 5 days)

This section was changed as a result of Modification 21.

Old Text:

The aim of the randomization visit is to assign blinded study treatment. Subjects may be randomized if they fulfill all study inclusion and exclusion criteria, have at least 80% adherence to both run-in study treatments, and remain committed to participate in the trial. Randomization activities ~~include~~:

- Perform run-in drug accountability; assess adherence to run-in drug (not applicable for subjects who are randomized ~~during the first week~~ after CABG surgery)
- Collect blood (DNA) sample for storage and central evaluation in COMPASS MIND substudy subjects

New Text:

The aim of the randomization visit is to assign blinded study treatment. Subjects may be randomized if they fulfill all study inclusion and exclusion criteria, have the blood results of the serum creatinine and total cholesterol available within 3 months of this visit, have at least 80% adherence (except for extenuating circumstances) to both run-in study treatments and remain committed to participate in the trial and randomization activities including:

- Perform run-in drug accountability; assess adherence to run-in drug (not applicable for subjects who are randomized Day 4-7 after CABG surgery)
- In patients randomized day 4-7 post CABG perform questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) at 1 month visit
- Assess local laboratory results of creatinine and total cholesterol
- Collect blood (DNA) sample for storage and central evaluation in COMPASS MIND substudy subjects, if applicable
- Record outcomes



Section 7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+)

This section was changed as a result of Modification 21.

Old Text:

- Perform CT angiography only at Visit 7 (1 year) in all subjects who are randomized during the first week after CABG (except in subjects ~~those~~ with specific contraindications)
 - Administer diet and activity questionnaires at Visit 9 (~~2 years~~)

New Text:

- In patients randomized Day 4-7 post CABG perform questionnaires (SAGE, DSS, MoCA, EQ-5D, Diet, and Physical Activity) (1 month).
- ...
- Perform CT angiography only at Visit 7 (1 year) in all subjects who are randomized during the first week after CABG to evaluate graft patency (except in subjects with specific contraindications). In the event the subject undergoes an invasive coronary angiography at 1 year post CABG for any reason, a CT angiogram may not be required.
 - Administer diet and activity questionnaires at Visit 9

Section 7.2.3 Other baseline characteristics

This section was changed as a result of Modification 4.

Old Text:

Validated health and quality of life questionnaires, SAGE, MoCA, DSS, EQ-5D will be administered at randomization, as well as Month 24, and the Final Follow-up Visit to measure the effect of randomized treatment on functional outcomes and quality of life, and diet and activity questionnaires will also be administered in order to explore the determinants and consequences of cognitive decline in patients with CAD and PAD.

New Text:

Validated health and quality of life questionnaires, SAGE, MoCA, DSS, EQ-5D will be administered at screening/run-in or randomization, as well as Month 24, and the Final Follow-up Visit to measure the effect of randomized treatment on functional outcomes and quality of life, and diet and activity questionnaires will also be administered in order to explore the determinants and consequences of cognitive decline in patients with CAD and PAD.

Section 7.3 Efficacy

This section was changed as a result of Modifications 2, 4 and 22.

**Old Text:**

The secondary efficacy outcome is a composite of myocardial infarction, stroke, cardiovascular death, venous thromboembolism, and cardiovascular hospitalization. Mortality by any cause is also a secondary efficacy outcome.

Tertiary efficacy outcomes include the evaluation of responses recorded for the SAGE, MoCA, DSS, and EQ-5D inventories and the following: individual components of the primary and secondary outcomes, hospitalization, ~~revascularization~~, amputation, unstable angina, worsening angina, new angina, heart failure, resuscitated cardiac arrest, new diagnosis of cancer.

MRU data will be incorporated into economic modeling, which will be performed and reported separately from this study.

The ~~primary~~ outcome for the pantoprazole randomization is a composite of 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 ~~from baseline~~, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, and gastrointestinal obstruction or perforation.

A detailed description of outcomes to be analyzed for this study will be provided in the separate statistical analysis plan.

New Text:

The secondary efficacy outcome is a composite of myocardial infarction, stroke, cardiovascular death, revascularization, venous thromboembolism, and cardiovascular hospitalization. Mortality by any cause is also a secondary efficacy outcome.

Tertiary efficacy outcomes include the evaluation of responses recorded for the SAGE, MoCA, DSS, and EQ-5D inventories and the following: individual components of the primary and secondary outcomes, hospitalization, amputation, stent thrombosis, unstable angina, worsening angina, new angina, heart failure, resuscitated cardiac arrest, new diagnosis of cancer, MRU, coronary artery bypass graft failure.

Hospitalization data will be collected on the CRF to permit the analysis of MRU. These data will be analyzed and reported to the sponsor separately and will include:

- Total days length of stay
- Emergency room visits
- Intensive care unit /cardiac care unit days
- Rehabilitation and skilled nursing facilities



- Reason for medical resource use, i.e., major adverse cardiovascular event or bleeding

MRU data will be incorporated into economic modeling, which will be performed and reported separately from this study.

The outcome for the pantoprazole randomization is a composite of 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, and gastrointestinal obstruction, or perforation.

A detailed description of outcomes to be analyzed for this study will be provided in the separate statistical analysis plan.

Section 7.5.1 Definition of (serious) adverse event

This section was changed as a result of Modification 23.

Old Text:

7.5.1 ~~International Conference of Harmonisation E6~~ Definition of (serious) adverse event

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity is a congenital anomaly / birth defect and/or is another medically important serious event representing a significant hazard, which is comparable to the aforementioned criteria.

New Text:

7.5.1 Definition of (serious) adverse event

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity is a congenital anomaly / birth defect and/or is another medically important serious event representing a significant hazard, which is comparable to the aforementioned criteria. A surgical procedure or hospitalization that was planned prior to signing of the informed consent by any physician treating the subject should not be recorded as an AE. However, the condition for which the surgery or hospitalization is required may be an AE.

Section 7.5.2 Casual relationship (new section)

This section was changed as a result of Modification 23.

**New Text:****7.5.2 Causal relationship**

The assessment of the causal relationship between an AE and the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF. The causality assessment should be done separately for each study treatment as detailed in the CRF. The assessment is based on the question whether there was a “reasonable causal relationship” to the study drug in question.

Section 7.5.3 Protocol-specific adverse event definitions

This section was changed as a result of Modifications 2, 22 and 23.

Old Text:

Rivaroxaban has been extensively studied in Phase 2 and 3 clinical studies involving more than 60,000 patients and its overall adverse event profile has been well described. Appropriate information concerning adverse events will be systematically collected and submitted to regulatory authorities and all data on safety and outcomes will be reviewed regularly by an unblinded Data and Safety Monitoring Board.

For the purposes of this trial, the following events will be captured on the CRF as study outcome events only and will be waived from unblinding and will be exempted from the expedited reporting but will be included in the final study report.

- Primary Outcomes:
 - Cardiovascular death
 - Myocardial infarction
 - Stroke
- Secondary and tertiary outcomes
 - Cardiovascular hospitalization
 - Venous thromboembolism
 - Revascularization
 - Amputation
 - Angina pectoris
 - Heart failure
 - Resuscitated cardiac arrest
 - New diagnosis of cancer

In addition, events that are expected to occur with high frequency in the population under study and for which no safety signal arose from the >60,000 patients already studied in



clinical trials with rivaroxaban will be captured on the CRF only, will be waived from unblinding, and will be exempted from expedited reporting. These include:

- Planned hospitalizations (e.g., for surgery, respite care)
- Non-cardiovascular SAEs (~~including unplanned hospitalizations~~) that are expected to occur with high frequency in the population under study (~~depression, pneumonia, trauma, chronic obstructive pulmonary disease, diabetes mellitus~~)

As bleeding, including fatal bleeding, from all tissues and organs is a known side effect of rivaroxaban, bleeding events, including those resulting in hospitalization, will not be reported as (S)AEs, but will be captured on the CRF only, and will be reported as outcomes.

~~Any other non-cardiovascular SAEs must be reported by the investigator to PPD within 24 hours and will be transmitted to the sponsor via expedited SAE reporting. The sponsor is responsible for reporting these events to the health authority.~~

In addition, any AEs of particular concern to the investigator may be recorded on the CRF to bring them to the attention of the sponsor.

Hospitalization data will be collected on the CRF to permit the analysis of MRU. These data will be analyzed and reported to the sponsor separately and will include:

- Total days length of stay
- Emergency room visits
- Intensive care unit /cardiac care unit days
- Rehabilitation and skilled nursing facilities
- Reason for medical resource use, i.e., major adverse cardiovascular event or bleeding

7.5.3.1 Adverse events of special safety interest

For ongoing pharmacovigilance, the large COMPASS trial is an opportunity to identify rare events in the population that may or may not be drug-related. The following events have, to date, not been observed with increased frequency with rivaroxaban, but are considered AEs of special safety interest. These events must be reported to PPD, independent of their seriousness, but within the same timelines as an SAE (within 24 hours) by reporting them on the SAE page of the CRF. Bayer HealthCare Global Pharmacovigilance may decide to upgrade the event based on the information received.

- ~~• A non-cardiovascular AE that recurs when the participant is restarted on study drug~~

New Text:

7.5.3.1 Protocol-specific exceptions to SAE reporting



Rivaroxaban has been extensively studied in Phase 2 and 3 clinical studies involving more than 70,000 patients and its overall adverse event profile has been well described.

Appropriate information concerning adverse events will be systematically collected and submitted to regulatory authorities and all data on safety and outcomes will be reviewed regularly by an unblinded Data and Safety Monitoring Board.

For the purposes of this trial, the following events will be captured on the CRF as study outcome events only and will be waived from unblinding and will be exempted from the expedited reporting but will be included in the final study report.

- Primary efficacy outcomes:
 - Cardiovascular death
 - Myocardial infarction
 - Stroke
- Secondary and tertiary efficacy outcomes
 - Cardiovascular hospitalization
 - Venous thromboembolism
 - Revascularization
 - Amputation
 - Stent thrombosis
 - Angina pectoris (unstable, worsening or new)
 - Heart failure
 - Resuscitated cardiac arrest
 - New diagnosis of cancer
 - Coronary artery bypass graft failure

- Primary safety outcomes:

As bleeding, including fatal bleeding, from all tissues and organs is a known side effect of rivaroxaban, bleeding events, including those resulting in hospitalization, will not be reported as (S)AEs, but will be captured on the CRF only, and will be reported as outcomes.

- Expected Events:

In addition, events that are expected to occur with high frequency in the population under study and for which no safety signal arose from the more than 70,000 patients already studied in clinical trials with rivaroxaban will be captured on the CRF only, will be waived from unblinding, and will be exempted from expedited reporting. These include:



- Planned hospitalizations (e.g., for surgery, respite care)
- Non-cardiovascular SAEs (including unplanned hospitalizations) that are expected to occur with high frequency in the population under study (depression, pneumonia, trauma, chronic obstructive pulmonary disease, diabetes mellitus)

Section 7.5.3.2 Reporting of (S)AEs

The following events are to be reported to PPD on the SAE/ESI CRF within 24 hours of the investigator becoming aware of the event/diagnosis Bayer HealthCare Global Pharmacovigilance is responsible for reporting these events to the health authority:

- Any non-cardiovascular death of a subject occurring after signing informed consent or prior to the end of monitoring for adverse events. (note: fatal bleeding events are primary safety outcomes and are exempted)
- Any non-cardiovascular SAEs not listed in Section 7.5.3.1
- Any non-cardiovascular AE that recurs when the subject is restarted on study drug (positive re-challenge).

In addition, any AEs of particular concern to the investigator may be recorded on the CRF to bring them to the attention of the sponsor.

7.5.3.3 Adverse events of special safety interest

For ongoing pharmacovigilance, the large COMPASS trial is an opportunity to identify rare events in the population that may or may not be drug-related. The following events have, to date, not been observed with increased frequency with rivaroxaban, but are considered AEs of special safety interest. These events must be reported to PPD, independent of their seriousness, but within the same timelines as an SAE (within 24 hours) by reporting them on the SAE page of the CRF. Bayer HealthCare Global Pharmacovigilance may decide to upgrade the event based on the information received.

Section 7.5.3.5 Pregnancies

This section was changed as a result of Modification 23.

Old Text:

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

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

**New Text:**

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

Section 7.5.3 Data Monitoring Board (section deleted):

This section was changed as a result of Modification 23.

Old text:**~~7.5.3 Data Safety Monitoring Board~~**

~~A DSMB will monitor the safety data in the study on an ongoing basis. Serious AEs that are outcome events (e.g., stroke, myocardial infarctions), or expected AEs associated with anticoagulation therapy (e.g. bleeding), or common events that are part of the natural history of the disease (as defined in Section 7.5.2) will be collected on the CRFs and evaluated by the DSMB. These events will not be collected on the SAE page in the CRF for expedited review or reporting. The details of this review will be defined in the DSMB charter.~~

Section 7.5.4 Reporting of events to Bayer by PPD and compliance with regulatory authorities' reporting requirements

This section was changed as a result of Modification 23.

Old Text:

SAEs that require expedited reporting described in Section 7.5.2 (protocol-specific adverse event reporting) are to be recorded on the appropriate SAE CRF page and are to be forwarded to PPD within 24 hours of the investigator having been made aware of the event. Upon receipt of this form it will be reported to Bayer Global Pharmacovigilance by PPD within 24 hours, or 3 calendar days for weekends or public holidays, or next working day whichever is earlier.

New Text:

Adverse events that require expedited reporting described in Section 7.5.3.2, 7.5.3.3 and 7.5.3.5 (protocol-specific adverse event reporting) are to be recorded on the appropriate SAE CRF page and are to be forwarded to PPD within 24 hours of the investigator having been made aware of the event. In this trial, exempted outcomes are to be recorded on the appropriate outcome CRF page, not the SAE CRF page. Upon receipt of an SAE CRF page this form will be reported to Bayer Global Pharmacovigilance by PPD within 24 hours, or 3 calendar days for weekends or public holidays, or next working day whichever is earlier.



Section 8.3.2 Secondary efficacy outcomes

This section was changed as a result of Modification 2.

Old Text:

- The composite of outcomes --- myocardial infarction, stroke, cardiovascular death, venous thromboembolism, and cardiovascular hospitalization

New Text:

- The composite of outcomes --- myocardial infarction, stroke, cardiovascular death, revascularization, venous thromboembolism, and cardiovascular hospitalization

Section 8.3.3 Tertiary and other efficacy outcomes

This section was changed as a result of Modification 2.

Old Text:

Section 8.3.3 Tertiary efficacy outcomes

The tertiary efficacy outcomes are:

...

- ~~Revascularization~~
- Amputation
- ...
- MRU

New Text:

Section 8.3.3 Tertiary and other efficacy outcomes

The tertiary efficacy outcomes are:

...

- Amputation
- Stent thrombosis
- ...
- MRU
- Coronary artery bypass graft failure

Section 8.3.5 Outcome for pantoprazole randomization

This section was changed as a result of Modification 4.

**Old Text:**

- Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL ~~from baseline~~

New Text:

- Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL

Section 8.3.6 Subgroup variables

This section was changed as a result of Modification 4.

Old Text:

Homogeneity of treatment effect 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 at Baseline~~ (yes, no)

New Text:

Homogeneity of treatment effect will be examined for the following subgroup variables:

- CAD (yes, no)
- PAD (yes, no)
- CAD and PAD (yes, no)
- CAD only, PAD only, CAD and PAD
- CABG days 4-7 before randomization (yes, no)

Section 8.4.5 Analysis of the outcome for pantoprazole randomization

This section was changed as a result of Modification 4.

Old Text:

Pantoprazole 40 mg od treatment group and 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 ~~primary~~ 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 ~~primary~~ outcome for at least one time point”.

**New Text:**

Pantoprazole 40 mg od treatment group and 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”.

Section 8.4.6 Subgroup Analyses

This section was changed as a result of Modification 4.

Old Text:

Subgroup analyses for the primary efficacy and safety outcomes, and the ~~primary~~ outcome for pantoprazole randomization will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes (Sections 8.4.1, 8.4.2, 8.4.3, 8.4.4 and 8.4.5).

New text:

Subgroup analyses for the primary efficacy and safety outcomes, and the outcome for pantoprazole randomization will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes (Sections 8.4.1, 8.4.2, 8.4.3, 8.4.4 and 8.4.5).

Section 8.6 Determination of sample size

This section was changed as a result of Modification 24.

Old Text:

In this trial, it is 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.

...

Assumptions for antithrombotic treatment randomization were:

- 3-arm study with 1:1:1 randomization
- In total, a minimum of ~~19,500~~ subjects are randomized (~~at least 6,500~~ subjects per treatment group)
- 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%
- Constant annual event rate in aspirin control group between ~~4.0%~~ and ~~4.5%~~



...

The expected total number of observed events and the estimated power for each of the two comparisons are displayed in Table 8-1.

Table 8-1. Events calculations

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

Based on these estimates and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban arms with at least 90% power, it is 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. In this multi-center study, each center is expected to randomize at least 50 subjects.

Assumptions for pantoprazole randomization are:

- Annual event 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 ~~14,000~~ subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in 1:1 ratio
- ...
- Under these assumptions, the expected total number of major upper gastrointestinal complications is between ~~300~~ and ~~580~~, depending on the observed event 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 implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis Software (SAS) macro provided by J. Shih (1995). In addition, simulations were performed to confirm that the Dunnett step-up testing procedure as described in Section 8.4.1 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).

**New Text:**

In this trial, it is planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome.

...

Assumptions for antithrombotic treatment randomization were:

- 3-arm study with 1:1:1 randomization
- In total, a minimum of 21,400 subjects are randomized (approximately 7,134 subjects per treatment group)
- 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%
- Constant annual event rate in 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 8-1.

Table 8-1. Events calculations

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

Based on these estimates and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban arms with at least 90% power, it is planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome. In this multi-center study, each center is expected to randomize at least 50 subjects.

Assumptions for pantoprazole randomization are:

- Annual event 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 12,840 subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in 1:1 ratio



...

Under these assumptions, the expected total number of major upper gastrointestinal complications is between 450 and 730, depending on the observed event 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 implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis System (SAS) macro provided by J. Shih (1995). In addition, simulations were performed to confirm that the Dunnett step-up testing procedure as described in Section 8.4.1 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).

Section 11.3 Publication policy

This section was changed as a result of Modification 25.

Old Text:

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. The study results will be reported irrespective of the outcome of the study. The Operations Committee will decide on the authorship of all papers. The main study results will be written by a writing group ~~lead~~ by members of the Operations Committee, and may include additional individuals who have made substantial and sustained contributions and will be on behalf of the whole study group.

New Text:

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. The study results will be reported irrespective of the outcome of the study. The Operations Committee which will also serve as a Publication Committee, will decide on the authorship of all papers. The main study results will be written by a writing group led by members of the Operations Committee, and may include additional individuals who have made substantial and sustained contributions and will be on behalf of the whole study group.

Section 12 References

This section was changed as a result of Modification 26.

Old Text:

- ~~1. Lloyd Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, de SG et al. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010 February 23;121(7):948-54.~~



- ~~2. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008 January 29;117(4):e25-146.~~

New Text:

1. Fact sheet: Cardiovascular diseases (CVDs): World Health Organization; 2013. Available from <http://www.who.int/mediacentre/factsheets/fs317/en/>
2. WHO. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008b.

Section 14.1 COMPASS MIND Substudy

This section was changed as a result of Modifications 4 and 27.

Old Text:

Design: A phase II trial seeking evidence of efficacy in which a convenience sample of 1500 COMPASS participants over age 65 undergo will be invited to participate – 500 assigned to each treatment arm, but balanced for age, prior stroke, and hypertension. Participants will undergo limited brain MRI sequences (Fluid Attenuated Inversion Recovery [FLAIR]), T-1 and T-2 sequences at entry and near end-study coupled with assessment of function (SAGE), and cognition (MoCA, digit symbol substitution). Recruitment will occur at COMPASS sites with access to high-quality (≥ 1.5 Tesla) reasonably-priced MR imaging. Images will be transmitted to the central MR imaging center via discs. Two-stage central interpretation blinded to treatment will be carried-out, with all incident covert infarcts confirmed by a second independent interpreter. The PPD has experience with collection and analysis of brain MRIs performed in substudies of several randomized trials: AVERROES, PURE, APOLLO, and (planned) TIPS 3 MIND.

Subjects will have DNA collected at baseline and blood collected at baseline and at the 1 month visit. The samples will be processed, and aliquots will be shipped for long-term storage in liquid nitrogen at the coordinating center in PPD. Blood samples will be processed and stored in such a way to allow future analysis of these aliquots for selected biomarkers, some of which have been observed in other studies to be predictors of stroke, and others which have a plausible association with cardiovascular outcomes. Detailed information concerning blood collection, processing, storage, and shipping is provided in the Manual of Operations.

Implications: The COMPASS MRI substudy ~~would be~~ the first randomized trial of an anticoagulant to prevent covert brain infarcts in patients with atherosclerotic vascular disease. Evidence that rivaroxaban reduces covert stroke better than or in addition to aspirin would have an immense potential public health impact. Within COMPASS trial, the MRI substudy



offers an opportunity to develop evidence of rivaroxaban efficacy for a separate clinical indication applicable to a burgeoning population.

New Text:

Design: A phase II trial seeking evidence of efficacy in which a convenience sample of 1500 COMPASS participants over age 65 undergo will be invited to participate – 500 assigned to each treatment arm, but balanced for age, prior stroke, and hypertension. Participants will undergo limited brain MRI sequences (Fluid Attenuated Inversion Recovery [FLAIR]), T-1, T-2, and T-2* GRE sequences at entry and near end-study coupled with assessment of function (SAGE), and cognition (MoCA, digit symbol substitution). Recruitment will occur at COMPASS sites with access to high-quality (≥ 1.0 Tesla) reasonably-priced MR imaging. Images will be transmitted to the central MR imaging center via discs. Two-stage central interpretation blinded to treatment will be carried-out, with all incident covert infarcts confirmed by a second independent interpreter. The PPD has experience with collection and analysis of brain MRIs performed in substudies of several randomized trials: AVERROES, PURE, APOLLO, and (planned) TIPS 3 MIND.

Subjects will have DNA collected at baseline and blood collected at baseline and at the 1 month visit. DNA and blood collections are optional (Section 7.1.1, 7.1.2.3 and 7.1.2.4.1). The samples will be processed, and aliquots will be shipped for long-term storage in liquid nitrogen at the coordinating center in PPD. Blood samples will be processed and stored in such a way to allow future analysis of these aliquots for selected biomarkers, some of which have been observed in other studies to be predictors of stroke, and others which have a plausible association with cardiovascular outcomes. Detailed information concerning blood collection, processing, storage, and ship

ping is provided in the Manual of Operations.

Implications: The COMPASS MRI substudy is the first randomized trial of an anticoagulant to prevent covert brain infarcts in patients with atherosclerotic vascular disease. Evidence that rivaroxaban reduces covert stroke better than or in addition to aspirin would have an immense potential public health impact. Within COMPASS trial, the MRI substudy offers an opportunity to develop evidence of rivaroxaban efficacy for a separate clinical indication applicable to a burgeoning population.

13.2 Amendment 8

13.2.1 Overview changes to the study

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

The following changes are introduced in Protocol Version 3.0.



Modification 1: Secondary and tertiary efficacy outcomes were revised.

Rationale: The secondary outcomes have been modified to include 2 composites of major thrombotic events, including new outcome components. These new composites were chosen to represent outcomes deemed to be most sensitive to the experimental antithrombotic treatment under investigation.

Sections affected:

- Synopsis: Study objectives
- Section 2 Study objectives
- Section 7.3 Efficacy
- Section 7.5.3.1 Protocol-specific exceptions to SAE reporting
- Section 8.3.2 Secondary efficacy outcomes
- Section 8.3.3 Tertiary and other efficacy outcomes

Modification 2: The multiple testing strategy was revised to ensure the control of the familywise type I error for both testing of primary and secondary efficacy variables.

Rationale: Originally it had been planned to use the step-up Dunnett procedure for the testing of the 2 primary outcomes to control the overall type I error level of 5% and to test secondary outcomes at the 5% level without any adjustment for multiplicity. Triggered by the FDA advice letter received in AUG 2014, this decision was revised to make use of the opportunity of a potential label claim for secondary outcomes if convincing results will be obtained. Since the Dunnett step-up test is not separable, the former testing strategy was replaced by 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.

Sections affected:

- Section 8.4 Statistical and analytical plans
- Section 8.4.1 Analysis of the primary efficacy outcome
- Section 8.4.2 Analysis of the secondary efficacy outcomes

Modification 3: Interim analysis revised.

Rationale: The statistical analysis plan for the interim analysis was corrected according to the advice received by the FDA in the letter received in AUG 2014. The description for the



analysis in the case where only 1 of the 2 interventional arms is continued after an interim analysis was updated.

Section affected:

- 8.5 Planned interim analyses

Modification 4: The number of subjects in the trial has been increased.

Rationale: During the first 2 years after randomization of the first subject, 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.

Sections affected:

- Synopsis: Number of subjects
- Section 4.1 Design overview
- Section 5 Study population
- Section 8.6 Determination of sample size

Modification 5: Emphasis was made that all subjects, including those who experience a primary study outcome, need to be followed to the scheduled end of the study.

Rationale: Some investigators are under the impression that subjects who experience MI or stroke no longer need to be followed up because they have already contributed to the study outcomes. This is not the case; all outcomes need to be collected until the end of the study.

Section affected:

- Section 5.2 Discontinuation of subjects from study treatment

Modification 6: Clarification was added regarding the start of interim study rivaroxaban/rivaroxaban placebo and the continued use of study aspirin/placebo.

Rationale: The protocol appeared to mandate the use of interim study rivaroxaban/rivaroxaban placebo in subjects who were treated with long-term dual antiplatelet therapy. This was never the intent; it is optional for investigators to commence subjects on interim study rivaroxaban/rivaroxaban placebo. This change to the protocol clarifies that it is optional.

Elsewhere in the protocol it is clearly indicated that study aspirin/placebo can be continued in subjects who are treated with dual antiplatelet therapy. This clarification has now also been included in this section.



Section affected:

- Section 6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting

Modification 7: Minor clarifications were made.

Rationale: Minor clarifications were made that do not affect the overall study concept.

Sections affected:

- Section 3.1 Study committees
- Section 4.3.1 Overall design rationale
- Section 6.3 Treatment assignment

Modification 8: The reference to a lack of an antidote for rivaroxaban was removed.

Rationale: A provision has been made for the future availability of a specific reversal agent for rivaroxaban.

Sections affected:

- Section 6.4.2.4 Guidance for the treatment of subjects who overdose on study rivaroxaban/rivaroxaban placebo
- Section 6.4.2.5 Guidance for the treatment of subjects who experience a major bleed

Modification 9: Text regarding post-study therapy was revised.

Rationale: At the beginning of the study, subjects are transitioned from non-study aspirin to experimental study treatment. At the end of the study they should be transitioned back to non-study aspirin. Other antithrombotic therapies are not approved as alternatives to aspirin and reference to their use at the end of the study is therefore being deleted.

Section affected:

- Section 6.8 Post-study therapy

Modification 10: Text regarding the concomitant use of aspirin/aspirin placebo was revised.

Rationale: The use of study aspirin/aspirin placebo in subjects who are treated with non-study aspirin or dual antiplatelet therapy is optional. As written in the previous version of the protocol, the implication was that this was mandatory but it has been clarified that it is optional. Also, study aspirin/aspirin placebo may be continued irrespective of the need for



other antithrombotic therapies; contrary to what was written in Section 6.9.1, aspirin/aspirin placebo does not have to be discontinued.

Sections affected:

- Section 6.9 Prior and concomitant therapy
- Section 6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors and CYP 3A4 inducers

Modification 11: Clarification was added regarding the reasons for planned hospitalizations/procedures and when they should be considered (S)AEs

Rationale: This revision reminds investigators that hospitalization planned prior to enrollment in the COMPASS trial should not be considered a SAE. This is not a change to the protocol; previously planned hospitalizations were never deemed to be SAEs.

Section affected:

- Section 7.5.1 E6 Definition of (serious) adverse event

Modification 12: Text was updated with revised data/results from newly published studies.

Rationale: To provide the most recent data.

Sections affected:

- Section 1.2.1 Rivaroxaban
- Section 1.2.2 Aspirin and anticoagulants
- Section 1.3 Benefit-risk assessment
- Section 4.3.1 Overall design rationale
- Section 7.5.3.1 Protocol-specific exceptions to SAE reporting
- Section 12 Reference list

Modification 13: Clarification was made when the questionnaires should be completed.

Rationale: The questionnaires are being used to measure the impact of study treatments on function and quality of life. This revision is aimed at ensuring that the questionnaires are also completed following major outcomes. This was inadvertently omitted from previous versions of the protocol.



Sections affected:

- Section 4.1 Design overview
- Section 7.1.1 Tabulated overview
- Section 7.2.3 Other baseline characteristics

Modification 14: For subjects who are randomized after CABG surgery, clarification was made as to when the first dose of study drug will be administered.

Rationale: The goal is to avoid use of study antithrombotic therapies within 12 hours of administration of non-study anticoagulants. The previous version of the protocol indicated that subjects should not be randomized until at least 12 hours after administration of any anticoagulant. After CABG surgery, subjects commonly receive a morning dose of anticoagulant prophylaxis and are then discharged later in the day. By not allowing randomization within 12 hours of anticoagulant, these subjects could not be randomized prior to discharge. With this revision they can still be randomized before discharge but they will still not receive the first dose of study anticoagulant until at least 12 hours after last administration of any anticoagulant.

Sections affected:

- Section 4.1.1 Subjects randomized after CABG surgery
- Section 6.4 Dosage and administration
- Section 6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery

Modification 15: Guidance for the management of subjects who develop stroke and who are being considered for reperfusion therapy was added.

Rationale: Investigators have asked for guidance about the management of subjects who develop an ischemic stroke and who are being considered for reperfusion therapy. In response to these requests, a section was added to the protocol as the topic was not addressed in the previous version.

New section:

- Section 6.4.2.6 Guidance for the treatment of subjects who develop a stroke and who are being considered for reperfusion therapy

Modification 16: An additional subgroup was added to those that will be examined: “Any prior CABG, further subdivided as CABG days 4-7 before randomization and other prior CABG”



Rationale: Approximately one-quarter of all subjects enrolled in COMPASS have had a prior CABG. We wish to separately examine outcomes in subjects with prior CABG and those who have not had prior CABG, to explore whether the effect of treatment is consistent in these subgroups. Similarly, within the CABG population we propose to explore the consistency of the treatment effect in those who were randomized early post-CABG and those who were randomized later post-CABG.

Section affected:

- Section 8.3.6 Subgroup variables

Modification 17: Revisions to the description and procedures of the COMPASS-MIND substudy were made.

Rationale:

a) It had been stated that the substudy would examine the effect of therapies on asymptomatic cerebral ischemia and bleeds. The reference to “asymptomatic” cerebral ischemia is inaccurate. These episodes of cerebral ischemia are not asymptomatic; rather, the symptoms are not attributed to the cerebral ischemia because the event is not recognized. These episodes of cerebral ischemia are thus better described as “covert.”

b) The substudy does not examine the effect of antithrombotic therapies on all bleeding events, just microbleeds. To avoid confusion the reference to bleeding assessment has been omitted.

c) As originally designed, the COMPASS MIND substudy was restricted to subjects over the age of 65 years because older subjects are more likely to have covert cerebral ischemia than those who are younger. The age cut off is, however, purely arbitrary. In order to simplify recruitment and increase generalizability of the results the age restriction has been removed.

d) The original timeframe for obtaining an MRI scan was within 3 months of randomization. This window is being expanded for the following reasons. First, at many sites the COMPASS MIND study is not approved until several months after the main study, thereby making some subjects already enrolled in the study at participating sites ineligible for the substudy. Second, there are sometimes delays in obtaining the MRI scan because of limited access to a scanner, and this has prevented some consented subjects from obtaining a scan within 3 months of randomization. While it is desirable to perform the scan as early as possible in order to maximize the period of exposure to study drug between scans, the opportunity to obtain a later scan will help to boost recruitment and this gain will outweigh any possible loss of statistical power resulting from a shorter time between the initial and the final scan. The revised protocol now indicates that MRI scan should be performed within 3 months or as soon as possible thereafter and at the end of the study.



Sections affected:

- Section 2 Study objectives
- Section 7.1.2.3 Randomization visit (Day 0 ± 5 days)
- Section 14.1 COMPASS MIND substudy

Modification 18: Text regarding the timing of CT angiograms for COMPASS CABG subjects has been added. Also, in the event that subjects are unable to attend a study visit in person, follow-up by telephone is acceptable.

Rationale: To provide some flexibility.

Sections affected:

- Section 4.1.1 Subjects randomized after CABG surgery
- Section 7.1.1 Tabulated overview
- Section 7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+)
- Section 9.3 Data processing

Modification 19: Text was revised to allow greater flexibility in the event a reduction of dose of study treatment is necessary.

Rationale: To provide more flexibility.

Section affected:

- Section 6.4.1 Dose modifications

13.2.2 Changes to protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment and “new text” displays the updated text. Deletions are ~~crossed out~~ and additions are underlined. Corrections of typing errors or editorial changes are not highlighted in this amendment.

Synopsis – Study objectives

This section was changed as a result of Modification 1.

**Old Text:**

Study objective(s)	<p>Secondary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> 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 (myocardial infarction, stroke, cardiovascular death, revascularization, and venous thromboembolism) and cardiovascular hospitalization compared with aspirin 100 mg od in subjects with CAD or PAD
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New Text:

Study objectives	<p>Secondary objectives for rivaroxaban randomization</p> <ul style="list-style-type: none"> 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: (1) <u>coronary heart disease death, myocardial infarction, ischemic stroke, acute limb ischemia</u>; (2) <u>cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia</u> compared with aspirin 100 mg od in subjects with CAD or PAD
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Synopsis – Number of subjects

This section was changed as a result of Modification 4.

Old Text:

Number of subjects	<p>Enrolled = approximately 23,500; randomized = 21,400 in approximately 30 countries worldwide</p> <p>Approximately 23,500 subjects will be enrolled; 21,500 will be admitted to the run-in period and 2000 subjects will undergo coronary artery bypass graft but no run-in. A non-compliance rate of 10% is anticipated for those subjects in the run-in period; thus, approximately 21,400 subjects will be randomized (approximately 19,400 subjects who completed run-in and 2000 who underwent coronary artery bypass graft without run-in) in approximately 30 countries worldwide.</p>
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New Text:

Number of subjects	<p>Enrolled = approximately <u>29,940</u>; randomized = <u>approximately 27,400</u> in approximately <u>33</u> countries worldwide</p> <p>Approximately <u>29,940</u> subjects will be enrolled; <u>approximately 28,300</u> will be admitted to the run-in period and 2000 subjects will undergo coronary artery bypass graft but no run-in. A non-compliance rate of 10% is anticipated for those subjects in the run-in period; thus, approximately <u>27,400</u> subjects will</p>
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be randomized (of which approximately 2000 subjects who underwent coronary artery bypass graft would be randomized without run-in) in approximately 33 countries worldwide.

Section 1.2.1 Rivaroxaban

This section was changed as a result of Modification 12.

Old Text:

Rivaroxaban has been tested in randomized controlled trials involving more than 70,000 patients and has been used by millions of patients worldwide.

New Text:

Rivaroxaban has been tested in randomized controlled trials involving more than 80,000 patients and has been used by millions of patients worldwide.

Section 1.2.2 Aspirin and anticoagulants

This section was changed as a result of Modification 12.

Added Text to end of 5th paragraph:

The PEGASUS trial demonstrated that 33 months of treatment with ticagrelor (90 mg twice-daily or 60 mg twice-daily) compared with placebo reduced the risk of cardiovascular death, myocardial infarction or stroke by 15-16% (ticagrelor 90 mg: 7.85%, ticagrelor 60 mg: 7.77%, placebo 9.04%; p=0.008 and p=0.004, respectively) in patients with a history of myocardial infarction 1 to 3 years earlier. This came at the cost of a 2-3 fold increase in major bleeding (ticagrelor 90 mg: 2.60%, ticagrelor 60 mg: 2.30%, placebo 1.06%; p<0.01 for each dose vs. placebo), and there was no reduction in total mortality (ticagrelor 90 mg: 5.15%, ticagrelor 60 mg: 4.69%, placebo 5.16%; p=0.99 and p=0.14, respectively). (43)

The DAPT trial randomized 9,961 patients with a history of coronary stenting with a drug eluting stent who had completed 12 months of dual antiplatelet therapy with a thienopyridine and aspirin to receive continuing clopidogrel 75 mg once daily or prasugrel 10 mg once daily or placebo for another 18 months. All patients continued receiving aspirin. Continuing treatment with a thienopyridine as compared with placebo reduced the rates of stent thrombosis by 71% (0.4% vs. 1.4%, p<0.001) and the composite, death, MI or stroke by 29% (4.3% vs. 5.9%, p<0.001) but at the cost of excess moderate or severe bleeding (2.5% vs. 1.6%, p=0.001) and a borderline significant 36% increase in all-cause death from any cause (2.0% vs. 1.5%, p=0.05). (44)

Excess mortality seen with extended dual antiplatelet therapy in the DAPT trial was confirmed in a subsequent meta-analysis of 10 randomized trials including 31,666 patients who had undergone coronary artery stenting comparing different durations of dual antiplatelet therapy. Shorter duration dual antiplatelet therapy was associated with an 18% reduction in



all-cause mortality (HR 0.82, 95% CI 0.69-0.98; p=0.02), predominantly due lower non-cardiac mortality (HR 0.67, 0.51-0.89; p=0.006), with similar cardiac mortality (HR 0.93, 0.73-1.17; p=0.52). Shorter duration dual antiplatelet therapy was also associated with a lower risk of major bleeding (HR 0.58, 0.47-0.72; p<0.001), but a higher risk of myocardial infarction (HR 1.51, 1.28-1.77; p<0.001) and stent thrombosis (HR 2.04, 1.48-2.80; p<0.001). (45)

Section 1.3 Benefit-risk assessment

This section was changed as a result of Modification 12.

Old Text:

In the ROCKET-AF trial, the 20 mg od dose was associated with an annualized rate of International Society on Thrombosis and Haemostasis (ISTH) major and non-major gastrointestinal (GI) combined bleeding rate of 2.23/100 patient years. (~~Sponsor data on file~~)

New Text:

In the ROCKET-AF trial, the 20 mg od dose was associated with an annualized rate of International Society on Thrombosis and Haemostasis (ISTH) major and non-major gastrointestinal (GI) combined bleeding rate of 3.2/100 patient years. (46)

Section 2 Study objectives

This section was changed as a result of Modifications 1 and 17.

Old Text (first secondary objective):

- 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 (~~myocardial infarction, stroke, cardiovascular death, revascularization, and venous thromboembolism) and cardiovascular hospitalization~~ compared with aspirin 100 mg od in subjects with CAD or PAD

Old Text (Substudy objectives):

The COMPASS-MIND substudy will examine the effect of the antithrombotic therapies being tested in COMPASS on ~~asymptomatic cerebral ischemia and bleeds~~, thereby providing additional information about mechanisms of disease and treatment benefits.

New Text:

- 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, acute limb ischemia; cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia) compared with aspirin 100 mg od in subjects with CAD or PAD



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.

Section 3.1 Study committees

This section was changed as a result of Modification 17.

Old Text:

An Operations Committee will be responsible for ensuring that study execution and management of the study are of the highest quality. This committee ~~will determine its own guidelines and approve the criteria and guidelines of the other committees.~~ The operations committee will convene regularly to discuss and report on the ongoing supervision of the study. The committee will consist of the study chair and principal investigators, project leader, senior study coordinator, 2-3 sponsor representatives, and 3-4 National Leaders (NL).

A Steering Committee comprising members of the Operations Committee, university-based and sponsor-based scientists with clinical and methodological expertise, and national leaders from each country, will be responsible for producing and conducting a scientifically sound study design and ensuring accurate reporting of the study. The steering committee will meet periodically to address and resolve scientific and practical issues encountered during the study.

An Events Committee consisting of members with clinical and methodological expertise will oversee the process of event ~~verification~~. The process of event ~~verification~~ is detailed in the Manual of Operations.

New Text:

An Operations Committee will be responsible for ensuring that study execution and management of the study are of the highest quality. This committee is a subcommittee of the Steering Committee and will convene regularly to discuss and report on the ongoing supervision of the study. The committee will consist of the study chair and principal investigators, project leader, senior study coordinator, 2-3 sponsor representatives, and 3-4 National Leaders (NL).

A Steering Committee comprising members of the Operations Committee, university-based and sponsor-based scientists with clinical and methodological expertise, and national leaders from each country, has overall responsibility for the study. The Steering Committee will be responsible for producing and conducting a scientifically sound study design and ensuring accurate reporting of the study. The steering committee will meet periodically to address and resolve scientific and practical issues encountered during the study.

An Events Committee consisting of members with clinical and methodological expertise will oversee the process of event adjudication. The process of event adjudication is detailed in the Event Adjudication Plan.



Section 4.1 Design overview

This section was changed as a result of Modifications 4 and 13.

Old Text:

This Phase 3, event-driven (at least 2,200 primary efficacy outcome events), randomized controlled trial will have a 3 x 2 partial factorial design and will randomize at least ~~21,400~~ subjects who will receive treatment for an expected average duration of 3 to 4 years.

....

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 treatment adherence, treatment interruption, outcomes, and adverse events (AEs). Validated questionnaires ~~will be administered before or at the time of randomization, or as soon as possible thereafter, and at Month 24 to collect data on subject health and quality of life (Standard Assessment of Global Activities in the Elderly [SAGE], Montreal Cognitive Assessment [MoCA], DSS [Digital Symbol Substitution], European Quality of Life-5 Dimensions [EQ-5D], The Interheart Diet Questionnaire, and The International Physical Activity Questionnaire).~~ 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. The Final Follow-up Visit will occur as soon as possible after the required pre-specified number of subjects experience a primary efficacy outcome event for the antithrombotic randomization (close out is expected to occur over a period of about ~~2~~ months). A final washout period visit (End of Washout Telephone Visit) will be conducted by telephone (performed 30 days after the Final 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. Bayer Global Pharmacovigilance will continue to follow the reported AEs until stabilized or resolved.

New Text:

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

....

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 treatment adherence, treatment interruption, outcomes, and adverse events (AEs). Validated questionnaires (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]) will be administered at screening/run-in or randomization, or as soon as possible thereafter, as well as at Month 24 and at the Final Follow-Up visit to collect data on subject health and quality of life. The SAGE, MoCA, DSS, and EQ-5D will also be administered at the next study clinic visit after each outcome event. The Interheart Diet Questionnaire and the International Physical Activity Questionnaire will be administered at screening/run-in or



randomization, or as soon as possible thereafter, and at Month 24. 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. The Final Follow-up Visit will occur as soon as possible after the required pre-specified number of subjects experience a primary efficacy outcome event for the antithrombotic randomization (close out is expected to occur over a period of about 3 months). A final washout period visit (End of Washout Telephone Visit) will be conducted by telephone (performed 30 days after the Final 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. Bayer Global Pharmacovigilance will continue to follow the reported AEs until stabilized or resolved.

Section 4.1.1 Subjects randomized after CABG surgery

This section was changed as a result of Modifications 14 and 18.

Old Text:

Subjects randomized Day 4-7 after CABG surgery will undergo the same screening, follow-up, and washout as other COMPASS trial subjects but not run-in. Subjects are to sign informed consent before or after the surgery.¹⁵ Randomization will occur between Day 4-7 15 after surgery, at least 24 hours following the removal of chest tubes ~~and~~ at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis) (Section 7.1.1 Tabulated overview).

Subjects randomized Day 4-7 after CABG surgery will undergo computed tomography (CT) angiography at 1 year as part of the study protocol to assess graft patency unless they have a specific contraindication for CT angiography (e.g., contrast allergy, estimated glomerular filtration rate <30 ml/min). In the event the subject undergoes an invasive coronary angiography at 1 year post CABG for any reason, a CT angiogram may not be required.

New Text:

Subjects randomized Day 4-7 after CABG surgery will undergo the same screening, follow-up, and washout as other COMPASS trial subjects but not run-in. Subjects are to sign informed consent before or after the surgery.¹⁵ Randomization will occur between Day 4-7 15 after surgery, at least 24 hours following the removal of chest tubes. The first dose of study drug should not be administered until at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis) (Section 7.1.1 Tabulated overview).

Subjects randomized Day 4-7 after CABG surgery will undergo computed tomography (CT) angiography at 1 year or later as part of the study protocol to assess graft patency unless they have a specific contraindication for CT angiography (e.g., contrast allergy, estimated glomerular filtration rate <30 ml/min). In the event the subject undergoes an invasive coronary angiography at approximately 1 year or later post CABG for any reason, a CT angiogram may not be required.



Section 4.3.1 Overall design rationale

This section was changed as a result of Modifications 7 and 12.

Added Text (5th paragraph) :

...In most cases, the benefit of the experimental treatment has either been of insufficient magnitude to warrant a switch in treatment (e.g., clopidogrel, prasugrel) or has been accompanied by a substantial excess of bleeding (e.g., vorapaxar, ticagrelor, warfarin).

Old Text (6th paragraph):

The use of aspirin-alone antiplatelet therapy (~~as provided as a comparator treatment in Arm C~~) for atherosclerotic CAD and PAD is ~~well-established~~. As such, most patients will be candidates for aspirin monotherapy. This is in line with current practice guidelines and the current prescribing information for secondary prevention. The dose of aspirin being tested in COMPASS is 100 mg/d.

New Text (6th paragraph):

The use of aspirin-alone antiplatelet therapy for atherosclerotic CAD and PAD is widely accepted. As such, most patients will be candidates for aspirin monotherapy. This is in line with current practice guidelines and the current prescribing information for secondary prevention. The dose of aspirin being tested in COMPASS is 100 mg/d.

Section 5 Study population

This section was changed as a result of Modification 4.

Old Text:

Approximately ~~23,500~~ eligible subjects will be admitted to the run-in period and an additional 2000 will be enrolled post CABG and without run-in. Approximately 10% of run-in subjects are expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study will randomize approximately ~~21,400~~ men and women with objectively confirmed CAD or PAD from approximately ~~30~~ countries worldwide.

New Text:

Approximately 28,300 eligible subjects will be admitted to the run-in period and an additional 2000 will be enrolled post CABG and without run-in. Approximately 10% of run-in subjects are expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study will randomize approximately 27,400 men and women with objectively confirmed CAD or PAD from approximately 33 countries worldwide.



Section 5.2 Discontinuation of subjects from study treatment

This section was changed as a result of Modification 5.

Old Text:

In all cases, including the subjects ~~with~~ the study outcome, every effort must be made to continue to follow the subject at regular study visits.

New Text:

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.

Section 6.3 Treatment assignment

This section was changed as a result of Modification 7.

Old Text:

For subjects who successfully complete the run-in period, the investigator or delegate will access the PPD randomization and drug management system to confirm eligibility ~~and that run-in rivaroxaban placebo bid and aspirin od have been stopped~~ and to obtain the randomized treatment allocation.

New Text:

For subjects who successfully complete the run-in period, the investigator or delegate will access the PPD randomization and drug management system to confirm eligibility and compliance to run-in rivaroxaban placebo bid and aspirin od and to obtain the randomized treatment allocation.

Section 6.4 Dosage and administration

This section was changed as a result of Modification 14.

Added Text:

....The first doses of study drug should be administered on the day of randomization, or at least 12 hours after the last dose of antithrombotic medication if being randomized post-CABG.



Section 6.4.1 Dose modifications

This section was changed as a result of Modification 19.

Old Text:

If there is concern that the subject may be intolerant of study treatments or if the subject is reluctant to take the full dose of study treatments, a possible approach to restarting study medications is to reduce the frequency of dosing to ~~once-daily or alternate-daily~~.

New Text:

If there is concern that the subject may be intolerant of study treatments or if the subject is reluctant to take the full dose of study treatments, a possible approach to restarting study medications is to reduce the frequency of dosing (eg, to once-daily or alternate-daily).

Section 6.4.2.2 Guidance for the treatment of subjects who require coronary artery bypass graft surgery

This section was changed as a result of Modification 14.

Old Text:

...Randomization should only be performed between Day 4-7 post-CABG and at least 24 hours following the removal of chest tubes ~~and~~ at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis).

New Text:

...Randomization should only be performed between Day 4-7 post-CABG and at least 24 hours following the removal of chest tubes. Study drug should not be administered until at least 12 hours after last administration of any anticoagulant (including DVT prophylaxis).

Section 6.4.2.3 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting

This section was changed as a result of Modification 6.

Old Text:

Subjects who remain on long term dual antiplatelet therapy ~~should~~ commence “interim study rivaroxaban/rivaroxaban placebo” once any non-study anticoagulant therapy is stopped.

**New Text:**

Subjects who remain on long term dual antiplatelet therapy may commence “interim study rivaroxaban/rivaroxaban placebo” once any non-study anticoagulant therapy is stopped. Study aspirin/placebo may be continued.

Section 6.4.2.4 Guidance for the treatment of subjects who overdose on study rivaroxaban/rivaroxaban placebo

This section was changed as a result of Modification 8.

Old Text:

~~A specific antidote for rivaroxaban is not available.~~ If rivaroxaban overdose is suspected, the use of activated charcoal up to 8 hours after overdose to reduce absorption may be considered. Due to its low solubility, rivaroxaban absorption plateaus at doses of 50 mg and above, thus limiting exposure in the majority of subjects. Gastrointestinal absorption of rivaroxaban is reduced in subjects exposed to high oral doses and thus the anticoagulant effect of an overdose of rivaroxaban is expected to be limited.

New Text:

If rivaroxaban overdose is suspected, the use of activated charcoal up to 8 hours after overdose to reduce absorption may be considered. Due to its low solubility, rivaroxaban absorption plateaus at doses of 50 mg and above, thus limiting exposure in the majority of subjects. Gastrointestinal absorption of rivaroxaban is reduced in subjects exposed to high oral doses and thus the anticoagulant effect of an overdose of rivaroxaban is expected to be limited. If available, consideration may be given to the use of a specific reversal agent.

Section 6.4.2.5 Guidance for the treatment of subjects who experience a major bleed

This section was changed as a result of Modification 8.

Old Text:

~~The management of bleeding in subjects receiving study rivaroxaban/rivaroxaban placebo is supportive, as rivaroxaban does not have a specific antidote.~~ Temporary discontinuation of rivaroxaban is expected to be sufficient to control bleeding in most cases because the drug half-life is only 5-13 hours. Local measures should be applied if needed to control bleeding (e.g., local pressure, endoscopy and injection of a bleeding vessel, embolization) and intravenous fluids and blood transfusion support should be provided as indicated. In the rare case of life-threatening bleeding, the investigator may consider obtaining advice from a hematologist. Animal studies suggest that both prothrombin complex concentrates and recombinant factor VIIa partially restore hemostasis following treatment with factor Xa inhibitors such as rivaroxaban and a randomized trial involving healthy subjects treated with



rivaroxaban has demonstrated that prothrombin concentrates reverse prolongation of the prothrombin time.(30) Rivaroxaban cannot be dialyzed as it is highly protein bound.

New Text:

Temporary discontinuation of rivaroxaban is expected to be sufficient to control bleeding in most cases because the drug half-life is only 5-13 hours. Local measures should be applied if needed to control bleeding (e.g., local pressure, endoscopy and injection of a bleeding vessel, embolization) and intravenous fluids and blood transfusion support should be provided as indicated. In the rare case of life-threatening bleeding, the investigator may consider obtaining advice from a hematologist. Animal studies suggest that both prothrombin complex concentrates and recombinant factor VIIa partially restore hemostasis following treatment with factor Xa inhibitors such as rivaroxaban and a randomized trial involving healthy subjects treated with rivaroxaban has demonstrated that prothrombin concentrates reverse prolongation of the prothrombin time.(30) Rivaroxaban cannot be dialyzed as it is highly protein bound. If available, consideration may be given to the use of a specific reversal agent.

Section 6.4.2.6 Guidance for the treatment of subjects who develop a stroke and who are being considered for reperfusion therapy (Section added)

This section was added as a result of Modification 15.

Added Text:

The decision to use reperfusion therapies (including intravenous, intra-arterial thrombolysis, or mechanical endovascular approaches) in acute ischemic stroke should follow local practice, experience, and guidelines. At present there are limited data to guide treatment in this setting in subjects taking rivaroxaban. The following guidance is intended to aid clinical decision making in this setting.

At or around the time of the peak drug levels (we suggest in the first 6 hours after a dose), clinicians may choose to unblind and to avoid thrombolysis if the subject is taking rivaroxaban. Alternatively, if it is possible to obtain a rivaroxaban anti-Xa level in this time period, clinicians may use this information to decide on the appropriateness of starting thrombolysis. Endovascular therapy with clot extraction can proceed whether or not the subject is receiving rivaroxaban without the need to unblind.

Section 6.8 Post-study therapy

This section was changed as a result of Modification 9.

Old Text:

At the conclusion of treatment with study medication, the study staff should encourage the subject to ~~begin~~ treatment with open-label aspirin ~~or other antithrombotic therapy~~, as indicated.

**New Text:**

At the conclusion of treatment with study medication, the study staff should encourage the subject to resume treatment with open-label aspirin as indicated.

Section 6.9 Prior and concomitant therapy

This section was changed as a result of Modification 10.

Old Text:

As described in Section 5.1.2, Exclusion Criteria, the use of the following agents is not permitted at study entry: systemic treatment with strong inducers of CYP 3A4 (e.g. rifampicin) and inhibitors of both CYP 3A4 and P-gp (e.g., systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir).

...

Study aspirin/aspirin placebo ~~should~~ be continued irrespective of the need for aspirin or dual antiplatelet therapy.

New Text:

As described in Section 5.1.2, Exclusion criteria, the use of the following agents is not permitted at study entry: systemic treatment with strong inducers of CYP 3A4 (e.g. rifampicin) and inhibitors of both CYP 3A4 and P-gp (e.g., systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir) (see Section 6.9.1).

...

Study aspirin/aspirin placebo may be continued irrespective of the need for aspirin or dual antiplatelet therapy.

Section 6.9.1 Combined CYP 3A4 and p-glycoprotein inhibitors and CYP 3A4 inducers

This section was changed as a result of Modification 10.

Old Text:

Strong inhibitors of both CYP 3A4 and p-glycoprotein increase plasma concentrations of rivaroxaban and are contraindicated in subjects taking rivaroxaban. These include systemic azole antifungal drugs (e.g. ketoconazole, itraconazole, posaconazole, etc.), and HIV protease inhibitors. Additionally, strong inducers of CYP 3A4 such as ~~i.e.~~ rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine can reduce the plasma concentrations of rivaroxaban. If any of these treatments are needed, randomized study rivaroxaban/rivaroxaban placebo ~~and aspirin/aspirin placebo~~ must be temporarily discontinued and open-label aspirin should be begun.

**New Text:**

Strong inhibitors of both CYP 3A4 and p-glycoprotein increase plasma concentrations of rivaroxaban and are contraindicated in subjects taking rivaroxaban. These include systemic azole antifungal drugs (e.g. ketoconazole, itraconazole, posaconazole, etc.), and HIV protease inhibitors. Additionally, strong inducers of CYP 3A4 such as rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine can reduce the plasma concentrations of rivaroxaban. If any of these treatments are needed, randomized study rivaroxaban/rivaroxaban placebo must be temporarily discontinued and open-label aspirin should be begun.

Section 7.1.1 Tabulated overview, Table 7-1

This section was changed as a result of Modifications 13 and 18.

Old Text:

	Pre-Screening ^a	Screening/ Run-in	Randomization ^s	Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Wash out
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m
Windows			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d
.....																		
MoCA, DSS, and SAGE		X ^o	X ^o	X ^p						X							X	

.....

h CT angiography will be performed at 1 year 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 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, ~~at the time of randomization (or soon thereafter, within 3 months)~~ and near the end of the follow-up

New Text:

	Pre-Screening ^a	Screening/ Run-in	Randomization ^s	Follow-up														Washout
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 ⁿ	Final	Wash out
Timing		-4w	0	1 m	3m ^m	6m	9m ^m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y		1 m post Final ^m
Windows			± 5d	± 7d	± 2w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 4w	± 5d
.....																		
MoCA, DSS, and SAGE [‡]		X ^o	X ^o	X ^p						X							X	

.....

- 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
-
- t. Also to be administered at the next study clinic visit after each outcome event



Section 7.1.2.3 Randomization visit (Day 0 ± 5 days)

This section was changed as a result of Modification 17.

Added Text:

- MRI of the brain will be performed only in COMPASS-MIND substudy subjects after randomization

Section 7.1.2.4.1 Routine follow-up visits (Visits 3, 5, and 7-15+)

This section was changed as a result of Modification 18.

Added Text:

- Perform CT angiography only at Visit 7 (1 year or later if not performed at 1 year) in all subjects who are randomized during the first week after CABG to evaluate graft patency (except in subjects 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.

...

While every effort should be made for the subject to attend those visits that are meant to be in person, infrequently it may not be possible to conduct the visit in person in which case the visit may occur by telephone instead.

Section 7.2.3 Other baseline characteristics

This section was changed as a result of Modification 13.

Old Text:

Validated health and quality of life questionnaires, SAGE, MoCA, DSS, EQ-5D will be administered at screening/run-in or randomization, ~~as well as Month 24,~~ and the Final Follow-up Visit to measure the effect of randomized treatment on functional outcomes and quality of life, ~~and~~ diet and activity questionnaires will also be administered in order to explore the determinants and consequences of cognitive decline in patients with CAD and PAD.

New Text:

Validated health and quality of life questionnaires (SAGE, MoCA, DSS, and EQ-5D) will be administered at screening/run-in or randomization, or as soon as possible thereafter, at Month 24 and at the Final Follow-up Visit, and at the next study clinic visit after each outcome event



to measure the effect of randomized treatment on functional outcomes and quality of life. Diet and activity questionnaires will also be administered at screening/run-in or randomization, or as soon as possible thereafter, and at Month 24 in order to explore the determinants and consequences of cognitive decline in patients with CAD and PAD.

Section 7.3 Efficacy

This section was changed as a result of Modification 1.

Old Text:

The secondary efficacy outcome is a composite of ~~myocardial infarction, stroke, cardiovascular death, revascularization, venous thromboembolism, and cardiovascular hospitalization~~. Mortality by any cause ~~is also a secondary efficacy outcome~~.

~~Tertiary~~ efficacy outcomes include the evaluation of responses recorded for the SAGE, MoCA, DSS, and EQ-5D inventories and the following: individual components of the primary and secondary outcomes, hospitalization, amputation, stent thrombosis, unstable angina, worsening angina, new angina, heart failure, resuscitated cardiac arrest, new diagnosis of cancer, MRU, coronary artery bypass graft failure.

...

~~A detailed description of outcomes to be analyzed for this study will be provided in the separate statistical analysis plan.~~

New Text:

The secondary efficacy outcomes are:

- a) a composite of coronary heart disease death, myocardial infarction, ischemic stroke or acute limb ischemia; and
- b) a composite of cardiovascular death, myocardial infarction, ischemic stroke or acute limb ischemia.
- c) mortality by any cause.

Other efficacy outcomes include the evaluation of responses recorded for the SAGE, MoCA, DSS, and EQ-5D inventories and the following: individual components of the primary and secondary outcomes, hospitalization, revascularization, amputation, stent thrombosis, unstable angina, worsening angina, new angina, heart failure, resuscitated cardiac arrest, venous thromboembolism, new diagnosis of cancer, MRU, coronary artery bypass graft failure.



Section 7.5.1 E6 Definition of (serious) adverse event

This section was changed as a result of Modification 11.

Old Text:

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity is a congenital anomaly / birth defect and/or is another medically important serious event representing a significant hazard, which is comparable to the aforementioned criteria. ~~A surgical procedure or hospitalization that was planned prior to signing of the informed consent by any physician treating the subject should not be recorded as an AE. However, the condition for which the surgery or hospitalization is required may be an AE.~~

New Text:

Note: If a subject is hospitalized or has a procedure that was planned or anticipated prior to the subject signing the informed consent, the hospitalization/procedure is considered part of medical history or a therapeutic intervention and is not the result of an (S)AE unless the severity has worsened or changed unexpectedly. Additionally, a procedure is not an (S)AE, but the reason for the procedure may be an (S)AE.

Section 7.5.3.1 Protocol-specific exceptions to SAE reporting

This section was changed as a result of Modifications 1 and 12.

Old Text:

Rivaroxaban has been extensively studied in Phase 2 and 3 clinical studies involving more than 70,000 patients and its overall adverse event profile has been well described.

...

- Secondary and tertiary efficacy outcomes
 - Cardiovascular hospitalization
 - Venous thromboembolism
 - Revascularization
 - Amputation
 - Stent thrombosis
 - Angina pectoris (unstable, worsening or new)
 - Heart failure



- Resuscitated cardiac arrest
- New diagnosis of cancer
- Coronary artery bypass graft failure

...

In addition, events that are expected to occur with high frequency in the population under study and for which no safety signal arose from more than ~~70,000~~ 80,000 patients already studied in clinical trials with rivaroxaban will be captured on the CRF only, will be waived from unblinding, and will be exempted from expedited reporting.

New Text:

Rivaroxaban has been extensively studied in Phase 2 and 3 clinical studies involving more than 80,000 patients and its overall adverse event profile has been well described.

...

- Secondary and tertiary efficacy outcomes
 - Coronary heart disease death
 - Ischemic stroke
 - Acute limb ischemia
 - Cardiovascular hospitalization
 - Venous thromboembolism
 - Revascularization
 - Amputation
 - Stent thrombosis
 - Angina pectoris (unstable, worsening or new)
 - Heart failure
 - Resuscitated cardiac arrest
 - New diagnosis of cancer
 - Coronary artery bypass graft failure

...



In addition, events that are expected to occur with high frequency in the population under study and for which no safety signal arose from more than 80,000 patients already studied in clinical trials with rivaroxaban will be captured on the CRF only, will be waived from unblinding, and be will be exempted from expedited reporting.

8.3.2 Secondary efficacy outcomes

This section was changed as a result of Modification 1.

Old Text:

The secondary efficacy outcomes are:

- The composite of outcomes — ~~myocardial infarction, stroke, cardiovascular death, revascularization, venous thromboembolism, and cardiovascular hospitalization~~
- Mortality (all-cause)

New Text:

The secondary efficacy outcomes are (in the following order):

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

Section 8.3.3 Tertiary and other efficacy outcomes

This section was changed as a result of Modification 1.

Old Text:

The tertiary efficacy outcomes are:

- Subject-reported SAGE, MoCA, DSS, and EQ-5D
- Individual components of the primary and secondary outcomes
- Hospitalization
- Amputation
- Stent thrombosis
- Unstable angina
- Worsening angina



- New angina
- Heart failure
- Resuscitated cardiac arrest
- New diagnosis of cancer
- MRU
- Coronary artery bypass graft failure

New Text:

The tertiary efficacy outcomes are:

- Subject-reported SAGE, MoCA, DSS, and EQ-5D
- Individual components of the primary and secondary outcomes
- Hospitalization for cardiovascular reasons
- Hospitalization
- Revascularization
- Amputation
- Stent thrombosis
- Unstable angina
- Worsening angina
- New angina
- Heart failure
- Venous thromboembolism
- Resuscitated cardiac arrest
- New diagnosis of cancer
- MRU
- Coronary artery bypass graft failure

Section 8.3.6 Subgroup variables

This section was changed as a result of Modification 16.

Added Text:

- Any prior CABG (yes, no), further subdivided as CABG days 4-7 before randomization and other prior CABG

Section 8.4 Statistical and analytical plans

This section was changed as a result of Modification 2.

Added Text:

Testing strategy

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 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. [Figure 1](#), these logical restrictions are represented by arrows.

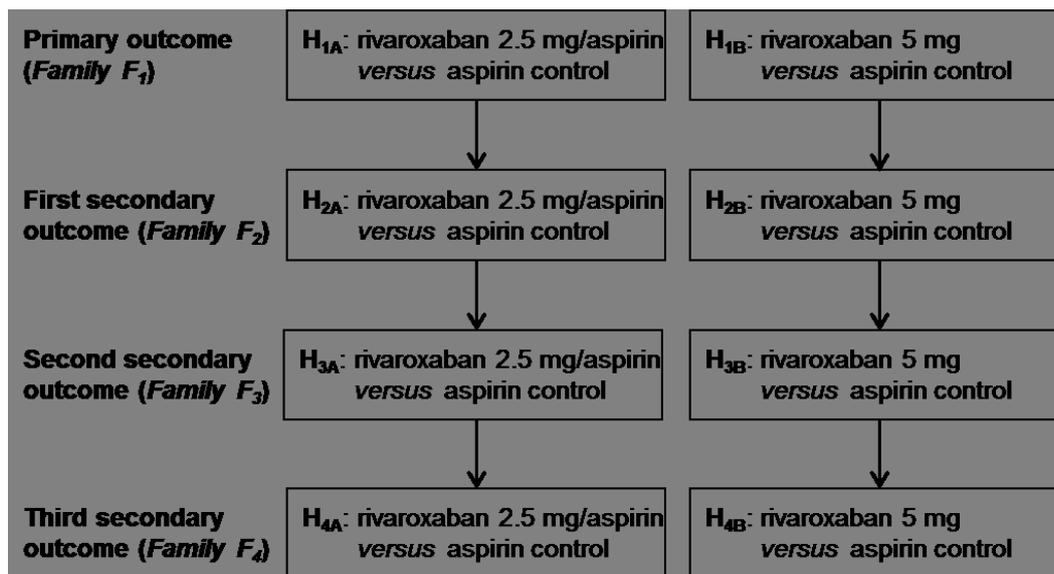


Figure 1: Hypothesis testing problem

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) was recently proposed in Brechenmacher et al., 2011. Details for the setting of this study will be described in the SAP.



Section 8.4.1 Analysis of the primary efficacy outcome

This section was changed as a result of Modification 2.

Old Text:

The 2 comparisons will be performed using 2 separate stratified log-rank tests. ~~A step-up Dunnett procedure(0,0) analogous to the Hochberg procedure will be used to control the overall type I error level of 5%. The asymptotically normally distributed log-rank test statistics will be ordered $|t_{(1)}| < |t_{(2)}|$ and compared to suitably defined critical values in a stepwise fashion starting with the smaller test statistic $|t_{(1)}|$. If $|t_{(1)}| \geq c_1 = 1.96$, i.e. if the larger of the two p -values is not greater than the 2-sided 5% type I error level, then both hypotheses will be rejected. Otherwise, the null hypothesis corresponding to the smaller test statistic $|t_{(1)}|$ will be retained and the larger test statistic $|t_{(2)}|$ will be compared to the larger critical value $c_2 = 2.223$, corresponding to a test at the 2-sided 2.63% type I error level.~~ 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. Study center will not be used as a stratification factor. 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.

.....

~~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. If the rivaroxaban-based treatment groups and aspirin control group are not significantly different in the analysis of the primary efficacy outcome but convincing evidence of the superiority of either of the 2 rivaroxaban-based antithrombotic regimens (e.g. a reduction of 3 standard deviations) is observed in the analysis of secondary efficacy outcomes, then such extreme differences will provide persuasive evidence of superiority of rivaroxaban-based antithrombotic therapy over aspirin-based therapy.~~

New Text:

The 2 comparisons will be performed using 2 separate stratified log-rank tests. Following the mixture gatekeeping procedure as mentioned in Section 8.4, a truncated Hochberg test with the pre-specified truncation parameter $\gamma = 0.9$ at $\alpha=0.05$ will be used. Further details will be described in the SAP. 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. Study center will not be used as a stratification factor. 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.

...



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.

Section 8.4.2 Analysis of the secondary efficacy outcomes

This section was changed as a result of Modification 2.

Old Text:

~~Analysis of the secondary efficacy outcomes will be based on the intention-to-treat principle (Section 8.2) and will use a similar approach as described in Section 8.4.1. 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 secondary analyses for multiple testing.~~

New Text:

Analysis of the secondary efficacy outcomes will be based on the intention-to-treat principle (Section 8.2) and will use a similar approach as described in Section 8.4.1. The family-wise error rate will be controlled using the truncated and/or regular Hochberg tests as described in Section 8.4 and more detailed in the SAP.

Section 8.5 Planned interim analysis

This section was changed as a result of Modification 3.

Old Text:

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 8.4.1 will be used in the final analysis; if the decision is made to continue with only one intervention, the final comparison will be made ~~at the 5% type I error level.~~

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-third~~ subjects with PAD; this will be monitored during the trial and steps may be taken to adjust the proportion during the trial.

New Text:

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 8.4 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:

- If one intervention was stopped early for efficacy, the multiple testing procedure for the final analysis will be performed as described in Section 8.4 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.
- If one intervention was stopped early for futility, the final analysis will be performed when at least 1,513* subjects in the 2 remaining arms have experienced an event. The final analysis will be performed according to the multiple testing strategy as described in Section 8.4. 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 a 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; this will be monitored during the trial and steps may be taken to adjust the proportion during the trial.



Section 8.6 Determination of sample size

This section was changed as a result of Modification 4.

Old Text:

In this trial, it is planned to randomize at least ~~21,400~~ subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome.

The aim is to achieve at least 90% power to detect a 20% relative risk reduction (RRR) for each of the 2 rivaroxaban-based treatment groups vs. the common aspirin control group. The total number of events needed is shown in Table 8–1 for different scenarios depending on the assumed annual ~~event~~ 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. If recruitment is going extremely well, a larger number of subjects may be recruited. All numbers below 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.

Assumptions for antithrombotic treatment randomization were:

- 3-arm study with 1:1:1 randomization
- In total, a minimum of 21,400 subjects are randomized (approximately 7,134 subjects per treatment group)
- 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%
- Constant annual ~~event~~ rate in aspirin control group between 3.0% and 4.0%
- 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 about 2.5 years
- Early discontinuation of study drug: about 6% and 4% in the 1st and 2nd 6-month periods, 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 8–1](#).

**Table 8-1. Events calculations**

Assumed annual event 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 and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban arms with at least 90% power, it is planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome. In this multi-center study, each center is expected to randomize at least 50 subjects.

Assumptions for pantoprazole randomization are:

- Annual event 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 ~~12,840~~ subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in 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 Final Follow-up Visit for each subject

Under these assumptions, the expected total number of major upper gastrointestinal complications is between 450 and 730, depending on the observed event 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 (40) implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis System (SAS) macro provided by J. Shih (1995).(41) In addition, simulations were performed to confirm that the ~~Dunnett step-up testing~~ procedure as described in Section 8.4.1 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).

New Text:

In this trial, it is planned to randomize at least 27,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome.

The aim is to achieve at least 90% power to detect a 20% relative risk reduction (RRR) for each of the 2 rivaroxaban-based treatment groups vs. the common aspirin control group. The total number of events needed is shown in Table 8–1 for different scenarios depending on the assumed annual incidence rate for the primary outcome in the aspirin group based on the assumptions modified according to Amendment 6 (integrated protocol Version 2.0), dated 03 JUL 2014. Due to the event-driven study design, the number of randomized subjects, length of enrollment and total study duration may vary. If recruitment is going extremely well, a larger number of subjects may be recruited. All numbers below 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-arm study with 1:1:1 randomization
- In total, a minimum of 21,400 subjects are randomized (approximately 7,134 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%
- Constant annual incidence rate in aspirin control group between 3.0% and 4.0%
- 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 about 2.5 years
- Early discontinuation of study drug: about 6% and 4% in the 1st and 2nd 6-month periods, 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 8–1](#).

**Table 8-1. Events calculations**

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 and the aim to detect a true relative risk reduction of 20% in each of the rivaroxaban arms with at least 90% power, it was planned to randomize at least 21,400 subjects and to continue the study until a minimum of 2,200 subjects experience an event for the primary efficacy outcome. In this multi-center study, each center is expected to randomize at least 50 subjects.

The originally planned sample size of 21,400 and 5 year study duration was based on an annual primary incidence rate in the control group of 3.5% and 90% power to detect a relative risk reduction of 20% in each of the rivaroxaban arms. Based on an observed incidence rate of 2.9% as of JUL 2015, it is now planned to randomize at least 27,400 subjects. This new sample size will maintain current study timelines and 90% power to detect a 20% relative risk reduction in each of the rivaroxaban arms, based on the following revisions to the original assumptions:

- Overall length of recruitment period about 3 to 3.5 years and taking observed randomization times up to July 2015 into account
- 2-sided overall type I error level of 5% using a truncated Hochberg test ($\gamma = 0.9$) for the testing of the 2 primary hypotheses
- Constant overall incidence rate of about 2.9% per year, resulting in a constant incidence rate of about 3.3% per year for the aspirin control group assuming a 20% relative risk reduction for both hypotheses
- Censoring due to non-CV death at an event rate of almost 1% per year

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 subjects included in the study are not proton pump inhibitor users and they are randomized to pantoprazole treatment and control groups in 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 Final Follow-up Visit for each subject

Under these assumptions, the expected total number of major upper gastrointestinal complications is between 570 and 780, depending on the observed event 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 (40) implemented in Power Analysis and Sample Size (PASS) software, version 11.0.7, and on a Statistical Analysis System (SAS) macro provided by J. Shih (1995).(41) In addition, simulations were performed to confirm that the mixture gatekeeping procedure as described in Section 8.4 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).

Section 9.3 Data processing

This section was changed as a result of Modification 18.

Added Text:

- Visit attendance

Section 12 Reference list

This section was changed as a result of Modification 12.

Deleted Text:

~~Dmitrienko A, Tamhane A, Bretz F (editors). Multiple Testing Problems in Pharmaceutical Statistics. Chapman and Hall/CRC, 2009.~~

~~Dunnett CW and Tamhane AC. A Step-Up Multiple Test Procedure. Journal of the American Statistical Association, 1992 87(417):162-170.~~

Added Text:

Brechenmacher, T, Xu, J, Dmitrienko, A, Tamhane, AC. A mixture gatekeeping procedure based on the Hommel test for clinical trial applications. Journal of Biopharmaceutical Statistics, 2011; 21: 748-767.



Dmitrienko, A, Tamhane, AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Statistics in Medicine, 2011; 30: 1473-1488.

Dmitrienko, A, Tamhane, AC. General theory of mixture procedures for gatekeeping. Biometrical Journal, 2013; 55: 402-419.

Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372:1791-1800.

Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlio DE, Steg PG, et al. Twelve of 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014; 371:2155-66.

Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trial. Lancet 2015;385:2371-82.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; Sep 8;365(10):883-91.

Section 14.1 COMPASS MIND Substudy

This section was changed as a result of Modification 17.

Old Text:

Hypotheses:

...

Pre-specified secondary outcomes would consider the effect of rivaroxaban on (1) non-lacunar covert brain infarcts; (2) all incident strokes, including clinical strokes (anticipated rate 1.2%/yr among peripheral arterial disease patients and 0.8%/yr among subjects with CAD), and all covert strokes; (3a) functional decline (Standard Assessment of Global-Activities in the Elderly [SAGE]) and (3b) cognitive decline (Montreal Cognitive Assessment [MoCA] and digit symbol substitution). Exploratory analyses will examine the predictive value of biomarkers (C-reactive protein, nt-proBNP) as independent predictors of covert brain infarcts.

Design: A phase II trial seeking evidence of efficacy in ~~which~~ a convenience sample of 1500 COMPASS participants ~~over age 65 undergo will be invited to participate~~— 500 assigned to each treatment arm, but balanced for age, prior stroke, and hypertension. Participants will undergo limited brain MRI sequences (Fluid Attenuated Inversion Recovery [FLAIR]), T-1, T-2, and T-2* GRE sequences ~~at entry~~ and near end-study coupled with assessment of function (SAGE), and cognition (MoCA, digit symbol substitution). Recruitment will occur at COMPASS sites with access to high-quality (≥ 1.0 Tesla) reasonably-priced MR imaging.



Images will be transmitted to the central MR imaging center via discs. Two-stage central interpretation blinded to treatment will be carried-out, with all incident covert infarcts confirmed by a second independent interpreter. The PPD has experience with collection and analysis of brain MRIs performed in substudies of several randomized trials: AVERROES, PURE, APOLLO, and (planned) TIPS 3 MIND.

Subjects will have DNA collected at baseline and blood collected at baseline and at the 1 month visit. DNA and blood collections are optional.(Section 7.1.1, 7.1.2.3 and 7.1.2.4.1) The samples will be processed, and aliquots will be shipped for long-term storage in liquid nitrogen at the coordinating center in PPD. Blood samples will be processed and stored in such a way to allow future analysis of these aliquots for selected biomarkers, some of which have been observed in other studies to be predictors of stroke, and others which have a plausible association with cardiovascular outcomes. Detailed information concerning blood collection, processing, storage, and shipping is provided in the Manual of Operations.

New Text:

Hypotheses:

...

Pre-specified secondary outcomes would consider the effect of rivaroxaban on (1) non-lacunar covert brain infarcts; (2) volume of white matter hyperintensities; (3) all incident strokes, including clinical strokes (anticipated rate 1.2%/yr among peripheral arterial disease patients and 0.8%/yr among subjects with CAD), and all covert strokes; (4a) functional decline (Standard Assessment of Global-Activities in the Elderly [SAGE]) and (4b) cognitive decline (Montreal Cognitive Assessment [MoCA] and digit symbol substitution). Exploratory analyses will examine the predictive value of biomarkers (C-reactive protein, nt-proBNP) as independent predictors of covert brain infarcts.

Design: A phase II trial seeking evidence of efficacy in a convenience sample of 1500 COMPASS participants with readable baseline MRI scans, 500 assigned to each treatment arm, but balanced for age, prior stroke, and hypertension. Participants will undergo limited brain MRI sequences (Fluid Attenuated Inversion Recovery [FLAIR]), T-1, T-2, and T-2* GRE sequences after randomization and near end-study coupled with assessment of function (SAGE), and cognition (MoCA, digit symbol substitution). Recruitment will occur at COMPASS sites with access to high-quality (≥ 1.0 Tesla) reasonably-priced MR imaging. Images will be transmitted to the central MR imaging center via discs. Two-stage central interpretation blinded to treatment will be carried-out, with all incident covert infarcts confirmed by a second independent interpreter. The PPD has experience with collection and analysis of brain MRIs performed in substudies of several randomized trials: AVERROES, PURE, APOLLO, and (planned) TIPS 3 MIND.

Some subjects, in participating centers, will have DNA collected at baseline and blood collected at baseline and at the 1 month visit. DNA and blood collections are optional.(Section



7.1.1, 7.1.2.3 and 7.1.2.4.1). The samples will be processed, and aliquots will be shipped for long-term storage in liquid nitrogen at the coordinating center in PPD . Blood samples will be processed and stored in such a way to allow future analysis of these aliquots for selected biomarkers, some of which have been observed in other studies to be predictors of stroke, and others which have a plausible association with cardiovascular outcomes. Detailed information concerning blood collection, processing, storage, and shipping is provided in the Manual of Operations.

14. Appendices

14.1 COMPASS MIND substudy - amended

Magnetic resonance imaging (MRI) substudy evaluating the incidence of clinically silent brain infarcts and subclinical brain ischemia (COMPASS-MIND)

Background: Clinically-evident strokes are the tip of the iceberg of vascular injury to the brain.⁽⁴²⁾ During the past decade, improvements in, and wider application of, magnetic resonance imaging (MRI) make it clear that subclinical (i.e., covert) strokes are more frequent than clinically-evident brain infarcts. In population-based cohorts with a mean age of 65 years, the prevalence of covert strokes is between 15% and 20% (i.e., several times the prevalence of symptomatic brain infarcts). Covert strokes are not benign; they are associated with cognitive and functional decline and are harbingers of future clinical strokes. Guidelines under development are likely to recommend that patients discovered to have covert strokes be treated aggressively regarding secondary prevention.

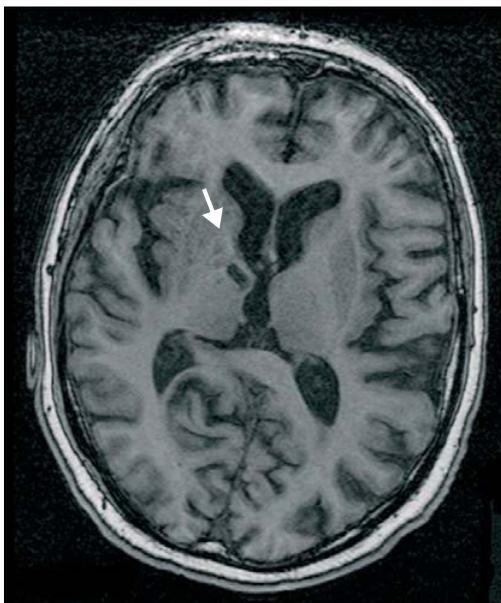


Figure 2: Covert brain infarct (arrow) on MR imaging (T-1 sequence)

Most covert brain infarcts in population-based studies are small subcortical strokes (often called lacunar infarcts) (see [Figure 2](#)) for which hypertension is the dominant risk factor. Because of their small size, such strokes are clinically unapparent if they do not involve motor or sensory tracts. In subjects with clinical vascular disease that will comprise the COMPASS trial cohort, the spectrum and underlying pathogenesis of covert strokes is unknown and may well be different from those in population-based studies.



There are no published randomized trials aimed at prevention of covert strokes. The AVERROES trial compared the novel oral anticoagulant apixaban with aspirin in atrial fibrillation patients deemed unsuitable for warfarin anticoagulation and included 1,185 patients who underwent brain MR imaging at entry. Covert brain infarcts were seen in 20%. The trial was terminated after only one year of follow-up due to efficacy, and the precipitous trial close-out resulted in repeat MR imaging in only 80% of those having an MRI at entry. The AVERROES MRI substudy (unpublished) was thus underpowered to determine the effect of apixaban on prevention of covert brain infarcts in atrial fibrillation patients deemed unsuitable for warfarin.

Prior epidemiologic investigations have demonstrated that selected biomarkers are significantly associated with the future development of cardiovascular events, including clinically evident strokes. Several of these markers (e.g., C-reactive protein) have been incorporated into clinical risk prediction models which assist clinicians in determining which patients are at low, moderate, or high risk of suffering a stroke. Further, our understanding of the mechanism of action of antithrombotic drugs has been increased by studying the effect of these therapies on biochemical markers associated with atherothrombosis. The COMPASS-MIND substudy provides a unique opportunity to examine biomarker as predictive of covert brain infarction and to understand how antiplatelet therapies and anticoagulants may modify this process. The main objective of COMPASS-MIND biomarker testing is to assess the association between selected biomarkers and the risk of overt and especially covert stroke in patients with established CAD and PAD. Markers to be measured include inflammatory markers (such as C-reactive protein), markers of neuronal injury (such as myelin basic protein, S-100B, neuron-specific enolase) and several miscellaneous markers (such as troponin, nt-proBNP) that have been shown to be powerful predictors of stroke in patients with atrial fibrillation. DNA collected in these same patients will enable exploration of the genetic determinants of stroke, including etiologic subtypes of stroke (cardioembolic, large vessel, small vessel disease) and in particular covert subcortical ischemia that is demonstrated on brain MRI and is associated with cognitive decline.

Hypotheses:

1. Treatment with rivaroxaban will reduce the incidence of covert brain infarcts (detected by blinded comparison of initial vs. end-study MRIs) compared with aspirin among patients with symptomatic atherosclerotic vascular disease involving the coronary and lower limb arteries.
2. The addition of rivaroxaban to aspirin will reduce the incidence of covert brain infarcts (detected by blinded comparison of initial vs. end-study MRIs) compared with aspirin among patients with symptomatic atherosclerotic vascular disease involving the coronary and lower limb arteries.

Pre-specified secondary outcomes would consider the effect of rivaroxaban on (1) non-lacunar covert brain infarcts; (2) volume of white matter hyperintensities; (3) all incident strokes, including clinical strokes (anticipated rate 1.2%/yr among peripheral arterial disease patients



and 0.8%/yr among subjects with CAD¹⁰⁰), and all covert strokes; (4a) functional decline (Standard Assessment of Global-Activities in the Elderly [SAGE]) and [4b] cognitive decline (Montreal Cognitive Assessment [MoCA] and digit symbol substitution).¹⁰¹ Exploratory analyses will examine the predictive value of biomarkers (C-reactive protein, nt-proBNP) as independent predictors of covert brain infarcts.

¹⁰²**Design:** A phase II trial seeking evidence of efficacy in a convenience sample of 1500 COMPASS participants with readable baseline MRI scans, 500 assigned to each treatment arm, but balanced for age, prior stroke, and hypertension. Participants will undergo limited brain MRI sequences (Fluid Attenuated Inversion Recovery [FLAIR]), T-1, T-2, and T-2*GRE sequences after randomization and near end-study coupled with assessment of function (SAGE), and cognition (MoCA, digit symbol substitution). Recruitment will occur at COMPASS sites with access to high-quality (≥ 1.0 Tesla¹⁰⁰) reasonably-priced MR imaging. Images will be transmitted to the central MR imaging center via discs. Two-stage central interpretation blinded to treatment will be carried-out, with all incident covert infarcts confirmed by a second independent interpreter. The PPD has experience with collection and analysis of brain MRIs performed in substudies of several randomized trials: AVERROES, PURE, APOLLO, and (planned) TIPS 3 MIND.

Some subjects, in participating centers, will have DNA collected at baseline and blood collected at baseline and at the 1 month visit.¹⁰³ DNA and blood collections are optional.(Section 7.1.1, 7.1.2.3 and 7.1.2.4.1)¹⁰⁰. The samples will be processed, and aliquots will be shipped for long-term storage in liquid nitrogen at the coordinating center in PPD. Blood samples will be processed and stored in such a way to allow future analysis of these aliquots for selected biomarkers, some of which have been observed in other studies to be predictors of stroke, and others which have a plausible association with cardiovascular outcomes. Detailed information concerning blood collection, processing, storage, and shipping is provided in the Manual of Operations.

Power: There is insufficient information in the literature to accurately estimate the incidence of covert brain infarcts for the COMPASS study cohort, but given a 3%/year incidence in population-based cohorts of similar age, 5%/yr in the aspirin arm is a conservative estimate. Given a sample size of 1500 participants randomized to 1 of 3 treatment arms (i.e. 500 patients in each treatment group), there will be approximately 70% power to assess a treatment effect of rivaroxaban of 45%. For the key pre-specified secondary analysis of the effect of rivaroxaban on the combined clinical and covert ischemic strokes with estimated incidence of 7% per year, the study power would be 0.72 to detect a 40% reduction and 0.85 to detect a 35% reduction. About 5% of participants will not undergo the second MRI due to acquiring a contraindication (e.g., pacemaker), death or refusal, so the power will be slightly less. These power calculations are based on a conservative estimate of the incidence of covert

¹⁰⁰ Text modified/added as per Amendment 6. (See Section 13.1.2)

¹⁰¹ Sentence revised with Amendment 8. (See Section 13.2.2)

¹⁰² Sentences revised with Amendments 6 and 8. (See Sections 13.1.2 and 13.2.2)

¹⁰³ Sentence revised with Amendment 8. (See Section 13.2.2)



brain infarcts during aspirin therapy in the COMPASS population, and higher rates would result in increased statistical power.

Implications: The COMPASS MRI substudy is the first randomized trial of an anticoagulant to prevent covert brain infarcts in patients with atherosclerotic vascular disease. Evidence that rivaroxaban reduces covert stroke better than or in addition to aspirin would have an immense potential public health impact. Within COMPASS trial, the MRI substudy offers an opportunity to develop evidence of rivaroxaban efficacy for a separate clinical indication applicable to a burgeoning population.