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**Statistical Analysis Plan**

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**A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction  
with EpaNova in HiGh Cardiovascular Risk PatienTs with  
Hypertriglyceridemia (STRENGTH)**

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**A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction  
with EpaNova in HiGh Cardiovascular Risk PatienTs with  
Hypertriglyceridemia (STRENGTH)**

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AstraZeneca

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**A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction  
with EpaNova in HiGh Cardiovascular Risk PatienTs with  
Hypertriglyceridemia (STRENGTH)**

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<b>TABLE OF CONTENTS</b>	<b>PAGE</b>
TITLE PAGE.....	1
SIGNATURE OF STUDY STATISTICIAN.....	2
SIGNATURE OF GLOBAL PRODUCT STATISTICIAN.....	3
TABLE OF CONTENTS.....	5
LIST OF TABLES.....	7
LIST OF ABBREVIATIONS.....	8
AMENDMENT HISTORY.....	10
1. STUDY DETAILS.....	16
1.1 Study objectives.....	16
1.1.1 Primary objective.....	16
1.1.2 Primary outcome measure.....	16
1.1.3 Secondary outcome measures.....	16
1.1.4 Tertiary outcome measures.....	17
1.1.5 Biomarker efficacy endpoints.....	17
1.1.6 Safety assessments.....	18
1.2 Study design.....	18
1.3 Number of patients.....	22
2. ANALYSIS SETS.....	22
2.1 Definition of Analysis Sets.....	22
2.1.1 Full Analysis Set (FAS).....	22
2.1.2 Safety Analysis Set (SAF).....	23
2.2 Deviations.....	23
3. PRIMARY AND SECONDARY VARIABLES.....	24
3.1 Adjudication of clinical endpoints.....	24
3.2 Baseline.....	24
3.3 Efficacy variables.....	24
3.3.1 Reference start date and study day.....	26
3.3.2 TTE calculation.....	26
3.3.3 Primary efficacy variable.....	26
3.3.4 Secondary efficacy variables.....	26
3.3.5 Tertiary outcome variables.....	28
3.3.6 Biomarker endpoints.....	28

3.4	Safety variables .....	29
3.4.1	Adverse Events .....	29
3.4.2	Bleedings.....	31
3.4.3	New onset of diabetes mellitus during the study .....	32
3.4.4	Laboratory tests.....	33
3.4.5	Vital signs .....	33
3.4.6	Electrocardiogram (ECG) .....	33
3.4.7	Physical examination .....	34
3.4.8	Overdoses.....	34
3.5	Additional variables .....	34
3.5.1	Demographic and other baseline characteristics.....	34
3.5.2	Medical history .....	35
3.5.3	Prior and concomitant medications.....	35
3.5.4	Duration of exposure.....	36
3.5.5	Treatment compliance.....	36
3.5.6	End-of-Study (EOS) assessment.....	37
3.6	Study Completers.....	37
4.	ANALYSIS METHODS .....	38
4.1	General principles .....	38
4.1.1	Study Periods .....	38
4.1.2	Visit Window and retests.....	39
4.1.3	Common calculations.....	41
4.1.4	Imputation rules and missing data .....	41
4.1.5	Patient disposition.....	44
4.1.6	Demographics and baseline characteristics.....	44
4.1.7	Medical history .....	44
4.1.8	Prior and concomitant medications.....	45
4.1.9	Duration of exposure.....	45
4.1.10	Treatment compliance.....	45
4.2	Analysis of efficacy outcome measures .....	45
4.2.1	Primary efficacy.....	45
4.2.2	Secondary outcome analyses .....	51
4.2.3	Tertiary outcome analyses .....	52
4.2.4	Exploratory outcome measures.....	54
4.2.5	Biomarkers Efficacy .....	54
4.3	Analysis of safety outcome measures .....	56
4.3.1	AEs.....	57
4.3.2	Bleedings.....	58
4.3.3	New onset of diabetes mellitus during the study .....	59
4.3.4	Laboratory Evaluations.....	59
4.3.5	ECG.....	61
4.3.6	Vital signs .....	61
4.3.7	Physical examination .....	61

4.3.8	Overdoses.....	62
5.	INTERIM ANALYSES .....	62
6.	CHANGES OF ANALYSIS FROM PROTOCOL .....	63
7.	REFERENCES .....	66
8.	APPENDICES .....	67
	APPENDIX 1 SUBGROUPS AND GEOGRAPHIC REGIONS .....	67
	APPENDIX 2 LIST OF LABORATORY TESTS .....	70
	APPENDIX 3 STATISTICAL MODELS.....	71
	Appendix 3.1 Cox proportional hazard model, Kaplan-Meier (KM) product-Limit method, event rates and hazard plots .....	71
	Appendix 3.2 Analysis of covariance model .....	73
	APPENDIX 4 TIMI BLEED CLASSIFICATIONS DERIVATION.....	74
	APPENDIX 5 PTS FOR TERTIARY OUTCOME ANALYSIS OF TOTAL THROMBOTIC EVENTS.....	78
	APPENDIX 6 PTS FOR CARDIOVASCULAR EVENTS.....	82

## List of Tables

Table 1	Schedule of Procedure .....	19
Table 2	Summary of time-to-events (TTE) endpoints.....	25
Table 3	Analysis Visits by Visit Window .....	40
Table 4	Marked abnormality criteria .....	61
Table 5	Interim Analysis Plan .....	63

## LIST OF ABBREVIATIONS

<b>Abbreviation or special term</b>	<b>Explanation</b>
5-point MACE	A composite MACE endpoint consisting of at least one of either cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina
AA	arachidonic acid
AE	adverse event
Apo B-100	apolipoprotein B-100
Apo C-III	apolipoprotein C-III
BILI	Total bilirubin
CEC	Clinical Events Committee
CI	confidence interval
CSP	Clinical study protocol
CSR	Clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DMC	Data Monitoring Committee
DPA	docosapentaenoic acid
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
EPA	eicosapentaenoic acid
ET	early termination
FAS	Full Analysis Set
FPFV	first patient first visit
GFR	glomerular filtration rate
HDL-C	high-density lipoprotein cholesterol



<b>Abbreviation or special term</b>	<b>Explanation</b>
HGR	Human Genetic Resources
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
IP	investigational product
KM	Kaplan-Meier
LDL-C	low-density lipoprotein cholesterol
MA	marked abnormality
MACE	major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization or hospitalization for unstable angina)
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Affairs
NNT	number needed to treat
PHL	potential Hy's Law
PIT	probability integral transformation
PT	preferred term
RBC	red blood cells
SAE	serious adverse event
SAF	Safety
SAP	statistical analysis plan
SBP	systolic blood pressure
SMQ	Standardised MedDRA Queries
SOC	system organ class
TC	total cholesterol
TG	triglycerides
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
TTE	time-to-event
VLDL	very low-density lipoprotein
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

## AMENDMENT HISTORY

Date	Brief description of change
22 <sup>nd</sup> Apr 2020	<ol style="list-style-type: none"> <li>1. Global product statistician updated.</li> <li>2. Amended list of abbreviations.</li> <li>3. In Section 1.1.5, clarified differences for high-sensitivity C-reactive protein analysis.</li> <li>4. In Section 2.2, disallowed used rather than prohibited and updated list of deviations.</li> <li>5. In Section 3.3, clarified how will be handled events with undetermined adjudication assessment.</li> <li>6. In Section 3.3.6, rectified timing of biomarker assessments.</li> <li>7. Section 3.4.1.8 deleted.</li> <li>8. In the bleeding event analysis, added a new category for bleeding event not categorizable due to missing data.</li> <li>9. Rectified starting point for HbA1c check in the definition of new onset of diabetes mellitus and added clarification about how to handle multiple signals of diabetes mellitus.</li> <li>10. MedDRA Dictionary and WHO-DD versions updated.</li> <li>11. In Section 3.4.8, changed definition of overdose.</li> <li>12. In Section 3.6, changed definition of study completers.</li> <li>13. Updated Table 3 and added in Section 4.1.2 details for visit name “Study terminated by sponsor”.</li> <li>14. Added more details in Section 4.1.4 for imputation rules on missing data and included bleeding events and new onset of diabetes mellitus.</li> <li>15. Deleted the last carried forward approach foreseen for Biomarkers, since no needed considering the windowing rules.</li> <li>16. In Section 4.1.10, added sensitivity analysis on treatment compliance.</li> <li>17. Amended Section 4.2.1.3.</li> <li>18. In Section 4.2.1.5, added a supplemental analysis with censoring at time of decision to early terminate the study and updated Section 6 accordingly.</li> <li>19. In Section 4.2.3, amended the joint frailty model to be used for recurrent events analysis.</li> <li>20. In Section 4.3.2, added analysis for location of bleeding events.</li> <li>21. In Section 4.3.4, added details on how local laboratory data are used for the analysis and changed time period for reporting of Hy’s Law cases.</li> </ol>

Date	Brief description of change
24 <sup>th</sup> Sept 2019	<ol style="list-style-type: none"> <li>1. Rephrased objectives as in the CSP, in Section 1.1.1, 1.1.2 and 1.1.3.2.</li> <li>2. Extended terms rather than abbreviations used for all endpoints and amended the list of abbreviations accordingly.</li> <li>3. Added to the list of abbreviations CSP, NNT and SMQ.</li> <li>4. Applied consistency in the reference to the dichotomous established cardiovascular disease at baseline variable.</li> <li>5. Amended Section 2.2 to be consistent with ICH E3 terminology on protocol deviation. Amended terminology for patients randomized more than once.</li> <li>6. Deleted Section on handling of patients randomized more than once.</li> <li>7. Added new Section 3.2 for definition of baseline.</li> <li>8. Clarified collection timing for biomarkers measures in Section 3.3.6</li> <li>9. Amended and clarified definition of completers in Section 3.6.</li> <li>10. Added multiple imputation scheme for the biomarker analyses in Section 4.1.4.</li> <li>11. Added imputation rules for missing/incomplete dates in Section 4.1.4.</li> <li>12. Amended definition of duration of exposure in Section 3.5.4.</li> <li>13. Amended definition of treatment compliance in Section 3.5.5.</li> <li>14. Added definition of study periods in Section 4.1.1.</li> <li>15. Moved description of the analysis of diabetes onset to Section 4.3.3 and changed to time to event analysis.</li> <li>16. Removed redundancy in the description of safety variables in Section 3.4 and added pregnancy test and overdoses.</li> <li>17. Removed terminology for treatment-emergent AEs and clarified timing for collection of AEs and SAEs.</li> <li>18. In Section 4.3.4 clarified that listing about abnormalities is based on MA criteria.</li> <li>19. Clarified that imputation rules for partial/missing dates will not be applied for listings in Section 3.4.1.</li> <li>20. Amended algorithm to identify AEs indicating diabetes in Section 3.4.3 and removed Appendix 5. Amended terminology for premature discontinuation of study medication in Section 4.1.5.</li> </ol>

21. Amended modelling language for clarity in Section 4.2.1.
  22. Added additional estimates to be presented in the KM analysis in Section 4.2.1.
  23. Created separate Section 4.2.1.1 for diagnostic procedures for the primary efficacy model.
  24. Added to the diagnostic procedures for the primary efficacy model the Cox-Snell residual plot and the diagnostic plots of hazard proportionality assumption for all the covariates in Section 4.2.1.1.
  25. Moved the analysis of on-treatment MACE events to Section 4.2.4 for exploratory outcome measure. Added in Section 6 the corresponding deviation from the protocol.
  26. Added a permutation-based approach to assess homogeneity of treatment effect in the subgroups analysis for primary outcome in Section 4.2.1.4.
  27. In Section 4.2.5 changed analysis from MMRM to ANCOVA, reflected in a reference to PROC GLM rather than PROC MIXED, for all the biomarkers. Added [Appendix 3.2](#). A for ANCOVA model description and clearly specified the natural log transformation for the outcome measures included. Added in Section 6 the corresponding deviation from the protocol. Clarified that high-sensitivity C-reactive protein will be analyzed as percent change from baseline to end of treatment. Added a last observation carried forward approach to the analysis and a multiple imputation scheme to assess impact of missing data.
  28. Clarified in Section 4.2.3 that the composite measure analysis will include all the events collected in the eCRF “Tertiary Endpoints” form and all those identified among the AEs collected.
  29. Extended the list of tertiary outcomes measures in Section 1.1.4 and 3.3.5, and added corresponding analysis details in Section 4.2.3.
  30. Clarified that bleeds will be classified programmatically. Added [Appendix 4](#) with corresponding algorithm. Added in Section 6 the corresponding deviation from the protocol. Moved analysis methods for bleedings into Section 4.3.2, amended censoring rule. Clarified that bleedings will not be adjudicated by CEC.
  31. Removed list of TFLs.
  32. Removed listings on vital signs, medical history, prior and concomitant medication and ECG in Section 3.4.5, 4.3.6, 4.1.7, 4.1.8, 4.3.5.
  33. Added definition and analysis details for overdoses in Section 3.4.8 and 4.3.8.
  34. Added TIA definition in Section 3.4.1.
  35. Added definition for AEs leading to dose reduction and IP interruption in Section 3.4.1.
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36. Added imputation rule for start and end date of study medication doses in Section 4.1.3. Also amended the last dose definition in Section 3.5.4 to consider also the “end date of study medication” from eCRF “Exposure” form.
  37. Moved Schedule of Procedure to Section 1.2.
  38. Moved Summary of time-to-event (TTE) endpoints to Section 3.3.
  39. Moved to Section 3.3.6 timing description for biomarkers collection.
  40. Amended wording for listing of safety variables in Section 3.4.
  41. Clarified timing of collection of AEs and SAEs in Section 4.3.1.
  42. Deleted definition of SAEs in Section 3.4.1.7.
  43. Added rule for imputation of partially missing or missing end date for AEs in Section 3.4.1.8.
  44. Added rule to identify patients without diabetes mellitus at baseline in Section 3.4.3.
  45. Added rule for analysis of laboratory test results reported as above or below the limit of quantification in Section 3.4.4.
  46. Clarified that Physical Examination data are not collected separately in Section 3.4.7.
  47. Removed from Section 3.5.1 safety variables and multiple risk factors.
  48. Moved Analysis Visits by Visit Window to Section 4.1.2.
  49. Clarified that prior and concomitant medication summaries will be reported separately and also for allowed and disallowed medications in Section 4.1.8.
  50. Clarified that data about administration of IP will be provided in listings in Section 4.1.9.
  51. Deleted analysis of compliance by visit.
  52. Added in Section 4.2.1.3 imputation rule for partially missing date of last contact.
  53. Removed Rosuvastatin subgroup from Section 4.2.1.4.
  54. Added in Section 4.3.1 summaries for on-treatment SAEs with event rates, on-treatment AEs with event rates.
  55. Added figures displaying maximum post baseline total bilirubin against maximum post baseline ALT and AST in Section 4.3.4.
  56. Added details for all subgroup variables in the [Appendix 1](#).
  57. Amended [Appendix 4](#) TIMI bleed classifications derivation.
  58. Added baseline estimated GFR and Ezetimibe treatment at baseline in Section 4.2.1.4.
  59. Time to all-cause death and corresponding subgroup analysis on patients with established cardiovascular disease at baseline added as key secondary measures. Added in Section 6 the corresponding deviation from the protocol.
  60. Added subgroup analyses in Section 4.3.1, 4.3.2 and 4.3.3.
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<b>Date</b>	<b>Brief description of change</b>
03 <sup>rd</sup> July 2019	<ol style="list-style-type: none"><li>1. Amended details for study statistician and global product statistician on signature page.</li><li>2. Clarified how time to onset of fatal myocardial infarction and stroke is derived in Sections 3.3.3 and 3.3.4.</li><li>3. Extended the list of secondary outcomes measures in the hierarchical testing to include subgroup analysis in Sections 1.1.3.1, 3.3.4 and 4.2.2 and added to Changes from Protocol in Section 6.</li><li>4. Added safety analysis of the patients with established cardiovascular disease at baseline to Section 3.4.1.</li><li>5. Amended censoring language for clarity in Section 4.2.1.3.</li></ol>

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<b>Date</b>	<b>Brief description of change</b>
29 <sup>th</sup> June 2018	<ol style="list-style-type: none"><li>1. Added 5-point MACE and 3-point MACE definitions to abbreviations and referenced throughout document.</li><li>2. Updated section 1.11 with explanation of endpoints.</li><li>3. New section 1.1 on handling of patients randomized more than once in analysis added.</li><li>4. Updated bleeding section with TIMI criteria in 3.4.2.</li><li>5. Added section 3.4.3 on Diabetes onset during study.</li><li>6. Updated the analysis visit windowing in section 4.1.3.</li><li>7. Added reference to Hy's Law and marked abnormality outputs in section 0 and Hy's Law in section 3.4.</li><li>8. Updated the statistical methodology for Biomarker Analysis in section 4.2.5.</li><li>9. Added in a note on systemic thromboembolism in section 1.1.1.</li><li>10. Added in biomarker efficacy and safety to Study Objectives in sections 1.1.5 and 1.1.6.</li><li>11. Added PHL and TIA to acronyms.</li><li>12. Updated text in PD section 2.2 to reflect that PDs will be identified prior to DBL but not necessarily all programmatically.</li><li>13. Updated PD list in section 2.2.</li><li>14. Added an additional summary on exposure in section 3.5.4.</li><li>15. Removed multiple risk factors from model in section 4.2.1.4.</li><li>16. Added Appendix 5 PTs for DIABETES ONSET DURING THE STUDY.</li><li>17. Clarified SAF population in section 1.1.</li><li>18. Refined censoring definition in section 4.2.1.3.</li><li>19. Added assessments used in censoring definition.</li><li>20. Clarified handling of deaths with undetermined cause in section 3.3.</li><li>21. Added section 3.6 on study completers.</li><li>22. Added derivation for handling multiple entries of same AE due to multiple hospitalizations in section 3.4.1.</li><li>23. Clarified in section 4.2.5 that back-transformed data will be presented.</li><li>24. Clarified in section 4.2.5 biomarkers are from plasma and RBC bioanalysis.</li><li>25. Added Kaplan-Meier for time from first dose of bleed in section 4.3.</li><li>26. Clarified AE summaries only include treatment-emergent AE in section 4.3.1.</li></ol>

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## **1. STUDY DETAILS**

### **1.1 Study objectives**

#### **1.1.1 Primary objective**

The primary objective of this study is to evaluate the effectiveness of adding Epanova to statin therapy (with or without ezetimibe) for lowering MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina) in high cardiovascular risk patients, with persistent hypertriglyceridemia and low high-density lipoprotein cholesterol.

#### **1.1.2 Primary outcome measure**

The primary outcome measure is the time to the first occurrence of any of the components of the composite of MACE.

#### **1.1.3 Secondary outcome measures**

##### **1.1.3.1 Key secondary outcome measures**

1. The composite measure of MACE that include the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
2. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
3. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the subgroup of patients with established cardiovascular disease at baseline.
4. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina.
5. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
6. Time to cardiovascular death.
7. Time to cardiovascular death in the subgroup of patients with established cardiovascular disease at baseline.
8. Time to all-cause death.
9. Time to all-cause death in the subgroup of patients with established cardiovascular disease at baseline.



### **1.1.3.2 Other secondary outcome measures (not included in hierarchical testing procedure)**

Other secondary outcome measures are:

- Emergent/elective coronary revascularization
- Hospitalization for unstable angina
- Fatal or non-fatal myocardial infarction
- Non-fatal myocardial infarction
- Fatal or non-fatal stroke
- Non-fatal stroke

### **1.1.4 Tertiary outcome measures**

Tertiary outcome measures are:

- The first occurrence of new onset atrial fibrillation.
- The composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systematic thromboembolism including arterial stent (except coronary) thrombosis or venous thromboembolism, i.e. deep vein thrombosis and/or pulmonary embolism.
- First occurrence of a heart failure event.
- The second, third, fourth, and total number occurrences of major cardiovascular events (primary and secondary outcome measures).
- The first CV-related hospitalization.

For an overall look of the study outcome measures, please refer to [Table 2](#). The standardized definition for endpoint events in cardiovascular trials can be found in protocol Appendix C.

### **1.1.5 Biomarker efficacy endpoints**

Biomarker efficacy endpoints will evaluate differences in change from baseline (Month 0) to Month 12 (primarily) between placebo (corn oil) and Epanova treatments.

In addition, biomarker data after Month 12 will be presented in a descriptive manner.

Biomarker variables include non-high-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, total cholesterol, very low density lipoprotein cholesterol, total cholesterol: high-density lipoprotein cholesterol ratio and calculated low density lipoprotein

cholesterol (in patients with triglycerides > 400 mg/dl low-density lipoprotein cholesterol will be directly measured), apolipoprotein B-100, apolipoprotein C-III, eicosapentaenoic acid , docosahexaenoic acid, docosapentaenoic acid and arachidonic acid in plasma and red blood cells, high-sensitivity C-reactive protein.

### **1.1.6 Safety assessments**

Safety assessments include adverse events, safety laboratory assessments, pregnancy tests and physical examinations.

## **1.2 Study design**

This study is a randomized, double-blind, placebo-controlled (corn oil), parallel group design that will enroll approximately 13,000 patients with hypertriglyceridemia and high risk for cardiovascular disease. It includes up to 3 Screening visits followed by a double-blind treatment period of approximately 3-5 years as determined when the number of patients with 5-point MACE outcomes is reached. This is an event-driven study and approximate 1,600 adjudicated primary outcome events are required. The treatment arms are balanced 1:1, Epanova: Placebo (corn oil) on top of a background of standard care (statin therapy).

It is estimated there are about 15 scheduled clinic visits, refer to [Table 1 Schedule of Procedures](#). There will be up to 3 Screening visits, depending on the need for repeated laboratory sample assessments or statin/ezetimibe adjustment. During the Screening period, patients will maintain a stable diet, and after randomization, be willing to adhere to the National Cholesterol Education Program Therapeutic Lifestyle Changes or equivalent diet.

Patients who meet all Inclusion Criteria and no Exclusion Criteria will be randomized. The randomization visit will be Month 0 followed by 11 treatment visits at Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60. There will be a 3-week follow-up visit after an early termination (ET) visit for those patients who undergo early permanent investigational product (IP) discontinuation due to a serious adverse event (SAE).

**Table 1 Schedule of Procedure**

Study Period	Screening <sup>2</sup>			Randomization and treatment					EOT/ET	EOT/ET Follow-up for SAE
	1	1a	1b	2	3	4	5	6 – 12	13	14
Month (±2 weeks)				0	3	6	12	18, 24, 30, 36, 42, 48 and 54	60 <sup>15</sup>	3 weeks after EOT/ET for SAE <sup>17</sup>
Informed Consent	X									
Medical History	X	X	X	X						
Prior Medications	X	X	X	X						
Physical Exam	X						X		X	
Clinical Assessments <sup>3</sup>	X	X	X	X	X	X	X	X	X	
Fasting Lipid Panel <sup>4,5</sup>	X	X	X	X			X <sub>3</sub> <sup>1</sup>	X <sup>13</sup>	X <sup>13</sup>	
Hemoglobin A <sub>1c</sub>	X			X			X <sub>3</sub> <sup>1</sup>	X <sup>13</sup>	X <sup>13</sup>	
Eligibility Review	X	X	X	X						
hs-CRP	X			X					X	
Serum Chemistry <sup>6</sup>	X			X			X	X <sup>7</sup>	X <sup>7</sup>	
TSH	X									
Urine Pregnancy Test <sup>8</sup>	X									
Fasting Plasma Glucose				X			X <sub>3</sub> <sup>1</sup>	X <sup>13</sup>	X <sup>13</sup>	
Hematocrit							X <sub>3</sub> <sup>1</sup>	X <sup>13</sup>	X <sup>13</sup>	
ECG				X						
Fasting Special Lipid Markers <sup>4,9</sup>				X			X		X	
Plasma and RBC Fatty Acids <sup>4,10</sup>				X			X		X <sup>10</sup>	
Fasting CV Risk Markers <sup>4,11</sup>				X	X					
Genetic sample <sup>14</sup>				X						

Counseling on TLC or Equivalent Diet	X									
AEs, Concomitant Medications and Endpoint Assessments <sup>12</sup>					X	X	X	X	X <sup>16</sup>	X <sup>18</sup>
Telephone Calls <sup>12</sup>										
Randomization				X						
Dispense IP				X	X	X	X	X		
Assess IP Compliance					X	X	X	X	X	

AE = adverse event;

EOT = End of treatment; EOT is defined for patients who 1) permanently discontinue IP before the study has ended but agree for further follow-up assessments (on-site visits or telephone or via third party) until end of study 2) complete Visit 12 (Month 60) and have not discontinued IP early;

ET = Early Termination. ET is defined for patients who permanently discontinue IP before the study has ended and decide **not** to participate with any follow-up assessments (on-site visits or telephone or via third party);

TSH = thyroid stimulating hormone;

hs-CRP = high-sensitivity C-reactive protein;

ECG = electrocardiogram;

CV = cardiovascular;

TLC = Therapeutic Lifestyle Changes;

IP = Investigational Product.

RBC= red blood cells

1. If fasting is not normal routine clinical practice, informed consent should be obtained prior to request for fasting for the Screening visit. If this is the case, the Screening visit should be split into 2 separate visits with informed consent obtained and IWRS accessed to obtain the patient number at the initial visit; and all other procedures obtained at the subsequent visit. In the event that the Screening visit is split into 2 separate visits, the screening visit lab draw must be completed within 3 days. At any subsequent visit, if the patient did not fast for the recommended 9-14 hours, the fasted lab may be drawn the next day.
2. If at Visit 1 the patient's TG, LDL-C, and HDL-C meet the inclusion criteria and the patient has been on a stable diet and has met all other inclusion criteria and none of the exclusion criteria the patient should return within 2 weeks for randomization at Visit 2.

If at Visit 1 the patient requires an adjustment to their statin regimen and/or a washout of other excluded lipid medications, the patient should return 4-6 weeks later to have their lipids re-drawn at Visit 1a.

If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications and either the patient's TG and/or HDL-C are borderline: TG >160 - 179 mg/dL (>1.81 – 2.02 mmol/L) or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) and/or HDL-C ≤45 mg/dL (1.17 mmol/L) for men and ≤50 mg/dL (1.30 mmol/L) for women, the patient can return within 2 weeks later to have all lipids re-drawn at Visit 1a.

If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications, and TG and HDL-C values are outside of borderline boundaries, the patient is considered screen failed.

The TG, LDL-C and HDL-C results from Visit 1a will be used to determine eligibility in the same way as for Visit 1. If re-drawn TG and HDL-C values are again borderline (as above), lipids can be repeated once more at Visit 1b to determine eligibility. Note that all lipid parameters qualifying for randomization should be obtained from the same visit.

The same process as for Visit 1a is applied for Visit 1b. If the TG, LDL-C and HDL-C criteria are not met after Visit 1b, the patient should be screen failed.

Please note the possibility to rescreen in the some situations, please see protocol section 6.4

3. Includes height (Visit 1 only), waist circumference and weight (Visit 1, 5, 7, 9, 11, 13 only), blood pressure, and heart rate.
4. Fasting blood samples should be drawn after the recommended 9-14 hour fast.
5. Lipid panel includes serum TG, TC, calculated LDL-C (in patients with triglycerides > 400 mg/dl LDL-C will be directly measured), HDL-C, calculated non-HDL-C, VLDL-C and TC: HDL-C ratio.
6. Serum chemistry includes creatine kinase, ALT, AST, total and direct bilirubin, and creatinine. Glomerular Filtration Rate (GFR) will be calculated only at Visits 1 and 5
7. Only ALT, AST and bilirubin will be analyzed, and only at Visits 7, 9, 11 and 13.
8. Females of childbearing potential only (see Exclusion No. 17).
9. Special lipid markers include serum apolipoprotein B-100 (Apo B-100), and apolipoprotein C-III (Apo C-III).
10. Plasma and RBC fatty acids (EPA, DHA, DPA and AA) will be measured from the recommended 9-14 hour fasting samples. Note: Plasma and RBC assessments are performed only at Visits 2 and 5, or ET before Visit 5.
11. Blood samples will be collected for future analyses on a subset of patients located in the US, of lipid fractions, inflammatory markers and other CV markers that may be identified during the course of the study.
12. In addition to these scheduled procedures, a well-being phone call will be made every 6 months ( $\pm 2$  weeks) starting after Visit 4 that will occur at Months 9, 15, 21, 27, 33, 39, 45, 51, and 57, except at scheduled visits, to question about adverse events, endpoint assessment, changes in medications and any major issues with the IP (losses or noncompliance). For further assessment of any identified potential or confirmed AE, a physical examination should be carried out if clinically appropriate.
13. Fasting lipid panel, Hb A<sub>1c</sub>, fasting plasma glucose and hematocrit will be measured annually at Visits 5, 7, 9, 11 and 13.
14. Genetic samples will be collected for future analysis on approximately 2000 patients in the US, see protocol Appendix F for details. The sample should preferably be taken at Visit 2. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit.
15. Patients who permanently discontinue taking IP for any reason will be asked to continue the regular study visits after the scheduled ET visit and (for permanent discontinuation of IP due

to SAE) the 3-week Follow-up visit unless they withdraw consent for further participation and the use of their data. In this case, patient will be asked to provide written documentation (when possible) of withdrawal of consent and complete the ET Visit procedures only. If the patient is permanently discontinued from study medication and agrees to continue in the protocol, then the patient, if possible, should have regularly scheduled study visits.

16. Patients who have early permanent discontinuation of IP due to an SAE and have an ET visit, will be required to schedule a 3-week Follow-up (Visit 14) to assess the SAE and concomitant medications. The patients should be asked to continue the regular study visits as described above thereafter.
17. Visit window is  $\pm 1$  week for Visit 14 (ET/EOT Follow-up for SAE).
18. At Follow-up Visit 14, other assessments from the procedures table may be performed upon investigator discretion to further evaluate the SAE causing ET or for SAE identified at EOT.

### **1.3 Number of patients**

This event-driven study is designed to have approximately 90% power to detect a 15% reduction in risk of primary efficacy 5-point MACE rate (hazard ratio [HR] = 0.85) for patients treated with Epanova when compared to placebo (corn oil), on top of a background of standard care (statin therapy). With an overall type I error rate (alpha level) of 5%, a total of 1,600 primary efficacy events are required for this study.

The enrolment of patients with documented CVD will be  $\geq 50\%$  of all randomized patients; the enrolment of patients with risk factors only (primary prevention) will be less than 50% of all randomized patients; these proportions will be monitored via interactive web response system.

Assuming total study duration of 4.5 years and a placebo (corn oil) event rate of approximately 4% per year, a sample size of 13,000 patients (6,500 per treatment arm) is required.

## **2. ANALYSIS SETS**

### **2.1 Definition of Analysis Sets**

#### **2.1.1 Full Analysis Set (FAS)**

The FAS will contain all patients who were randomized. Patients will be analyzed according to the treatment arm to which they were randomized (not according to the treatment arm actually received). If randomized more than once, the enrolment code at first randomization will be included in the FAS.

The notation of FAS will be used interchangeably with the notation of intent-to-treat population from the protocol, and this change is also documented in [Section 6](#).

### **2.1.2 Safety Analysis Set (SAF)**

The SAF will contain all randomized patients who received at least 1 dose of IP. Patients will be analyzed according to their randomized treatment. Patients who are given treatment different to their randomized treatment will be listed in the protocol deviations summary.

## **2.2 Deviations**

As defined by ICH E3, protocol deviations are any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are those protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or wellbeing.

All important protocol deviations will be summarized and listed by randomized treatment arm.

Protocol deviations pertaining (but not limited) to the following categories are considered to be Important:

- Patients who were randomized but did not meet inclusion and exclusion criteria.
- Patients who received disallowed concomitant medications and dietary products.
- Patients who either enrolled into the study more than once or enrolled into another interventional (pharmacologic agent or device - observational/non-interventional trial enrolment is permitted) clinical trial in parallel to this study.
- Patients who received the wrong study treatment at any time during the study.
- Patients who took < 80% of total scheduled study treatment whilst on study treatment.
- Patients who become pregnant and for whom IP is not discontinued.
- Patients with ALT or AST  $\geq 3xULN$  and total bilirubin (BILI)  $\geq 2xULN$  elevation (and in which the elevation in transaminases precedes or on the same day as the elevation in BILI) on or after the first dose of study medication for whom IP is not discontinued.
- Patients who had no written informed consent provided.

This list is not intended to be all-inclusive. Other protocol deviations may be identified as important by the study team during on-going review of the study prior to treatment unblinding. Important protocol deviations will be documented in a separate PD plan.

FAS will be used for the primary analysis therefore protocol deviations will not imply exclusion from the analysis. No analysis on a Per-Protocol population is planned for this study.

### **3. PRIMARY AND SECONDARY VARIABLES**

#### **3.1 Adjudication of clinical endpoints**

An independent Clinical Events Committee (CEC) will systematically identify and adjudicate all components of the primary and secondary endpoints as well as the tertiary heart failure event endpoint. Events will be analyzed per pre-specified definitions provided in a separate CEC charter and will be agreed upon by the CEC and the Executive Committee. Standardized definitions for endpoint events are provided by the Standardized Data Collection for Cardiovascular Trials Initiative (CSP Appendix C: Standardized Definitions for Endpoint Events in Cardiovascular Trials).

In this study, 5-point MACE is defined as a composite measure of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization and hospitalization for unstable angina. Primary efficacy endpoints in the study will not be reported to health authorities as SAEs. Events identified as suspected MACE-endpoints will be reported on a separate event form in the electronic case report form (eCRF) to support central adjudication. Clinical data reported as adverse events (AEs)/SAEs will be reviewed for possible endpoint events.

#### **3.2 Baseline**

Baseline is defined as the last non-missing measurement taken on or prior to date of randomization (including unscheduled assessments).

#### **3.3 Efficacy variables**

The efficacy objectives will be evaluated using analysis of time from randomization to the first event, using only events positively adjudicated by CEC. Events with undetermined adjudication assessment will be considered as positively adjudicated. Deaths with undetermined cause will be counted as cardiovascular deaths for primary composite endpoint as well as all secondary endpoints involving cardiovascular death. Time will be calculated as the number of days plus 1 between the date of randomization and date of the first occurrence of the event, or, if no event has occurred, the date of censoring will be used. Censoring rules are further described in [Section 4.2.1.3](#).

In order to facilitate describing various time-to-event (TTE) analyses the following table accounts for all endpoints.



**Table 2 Summary of time-to-events (TTE) endpoints**

Description	Primary (MACE)	Secondary										Tertiary <sup>3</sup>						
		KEY <sup>1</sup>				Other (exploratory) <sup>2</sup>												
cardiovascular death <sup>4</sup>	X	X		X														
cardiac death <sup>5</sup>			X															
non-fatal myocardial infarction	X	X	X						X									
myocardial infarction (fatal or non-fatal)								X										
non-fatal stroke	X	X										X						
stroke (fatal or non-fatal)											X							
emergent/elective coronary revascularization	X		X			X												
hospitalization for unstable angina <sup>6</sup>	X		X				X											
all-cause death					X													
atrial fibrillation													X					
coronary stent thrombosis														X				
systematic thromboembolism <sup>7</sup>														X				
venous thromboembolism/pulmonary embolism														X				
heart failure																X		
CV-related hospitalization																		X

<sup>1</sup>Note: Key secondary endpoints are those that are tested in a hierarchical order to preserve the alpha level. The Primary endpoint and all key secondary endpoints are also evaluated in the subgroup of patients with established cardiovascular disease at baseline. Those tests are also performed under Type I error control, see [Section 3.3.4](#) for the exact testing hierarchy.

<sup>2</sup>Note: Other secondary endpoints are the individual components of the primary composite, which are not part of the hierarchical testing procedure and therefore should be regarded as exploratory.

<sup>3</sup>Note: Tertiary endpoints are exploratory endpoints which do not consist of components of the primary.

<sup>4</sup>Note: Cardiovascular death includes death resulting from: an acute myocardial infarction (fatal or non-fatal myocardial infarction), sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes. Deaths with undetermined cause are included in the cardiovascular category.

<sup>5</sup>Note: Cardiac death includes death resulting from: an acute myocardial infarction, sudden cardiac death, death due to cardiovascular procedures.

<sup>6</sup>Note: The analysis date for the start of the hospitalization for unstable angina is the date that the patient was hospitalized for hospitalization for unstable angina

<sup>7</sup>Note: Systemic thromboembolism includes arterial stent (except coronary) thrombosis

### 3.3.1 Reference start date and study day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the date of randomization, Day 1 is the day of randomization, and Day -1 is the day prior to the date of randomization.

- If the date of the event is on or after the reference date then:

Study Day = date of event – date of randomization + 1 day.

- If the date of the event is prior to the reference date then:

Study Day = date of event – date of randomization.

When converting the number of days to other units, the following conversion factors will be used: 1 year = 365.25 days; 1 month = 30.4375 days.

### 3.3.2 TTE calculation

Unless noted otherwise, the reference start day for TTE analysis will be based on the date of randomization:

- $TTE \text{ (months)} = (\text{date of event} - \text{date of randomization} + 1 \text{ day}) / 30.4375$

### 3.3.3 Primary efficacy variable

The primary outcome measure is time to first occurrence of any component of the composite of 5-point MACE events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization or hospitalization for unstable angina; [Table 2](#))

An index myocardial infarction or stroke can lead to a death occurring at a later time point and therefore the time to event calculation for fatal myocardial infarctions and fatal strokes will be defined as follows:

Time to event will be calculated as the time from date of randomization to the date on which the index event (myocardial infarction or stroke) leading to death happened, if occurring on a separate day than death. If death occurred on the same day, this is the fatal event date used to calculate time to event.

### 3.3.4 Secondary efficacy variables

The key secondary variables, which will be tested in hierarchical order, are time-to the first occurrence of:

1. The composite measure of MACE that include the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
2. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
3. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the subgroup of patients with established cardiovascular disease at baseline.
4. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina.
5. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
6. Cardiovascular death.
7. Cardiovascular death in the subgroup of patients with established cardiovascular disease at baseline.
8. All-cause death.
9. All-cause death in the subgroup of patients with established cardiovascular disease at baseline.

Other secondary variables are time-to:

- emergent/elective coronary revascularization
- hospitalization for unstable angina
- fatal or non-fatal myocardial infarction
- non-fatal myocardial infarction
- fatal or non-fatal stroke
- non-fatal stroke

Time to event calculations for fatal myocardial infarctions and strokes will be handled as detailed in [Section 3.3.3](#).

This applies to endpoints where myocardial infarctions and/or strokes are included. In analyses of time to cardiovascular death or time to death, the time to event calculation will use the actual death date.

For an overall look of the secondary efficacy variables, please refer to [Table 2](#).

### 3.3.5 Tertiary outcome variables

Tertiary variables include:

- Time to first occurrence of new onset atrial fibrillation.
- Time to the composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systemic thromboembolism including arterial stent (except coronary) thrombosis or venous thromboembolism, i.e. deep vein thrombosis and/or pulmonary embolism.
- Time to first occurrence of a heart failure event.
- The second, third, fourth, and total number occurrences of major cardiovascular events (primary and secondary outcome measures).
- The time to first CV-related hospitalization.

CV-related hospitalization is defined as any hospitalization related to an adjudicated endpoint (MACE or heart failure) or a cardiovascular AE. A cardiovascular AE is defined by the list of Preferred Terms in [Appendix 6](#).

The time to hospitalization will be from randomization to admission according to the calculation in [Section 3.3.2](#). If admission date is incomplete or missing, it will for purposes of analysis be imputed according to the following rules:

- If the admission date is incomplete, the earliest possible date is compared to the AE onset date and the latest of these dates is imputed. The earliest possible date is defined as the first day of the month if only the day part of the admission date is missing or January 1st if both day and month are missing from the admission date.
- If admission date is missing, the AE onset date is imputed.

For an overall look of the tertiary efficacy variables, please refer to [Table 2](#).

### 3.3.6 Biomarker endpoints

Biomarker parameters include:

- Non-high-density lipoprotein cholesterol, triglycerides and high-density lipoprotein cholesterol;
- Total cholesterol, very low-density lipoprotein cholesterol, total cholesterol: high-density lipoprotein cholesterol ratio and low-density lipoprotein cholesterol;
- Apolipoprotein B-100 and apolipoprotein C-III;

- Eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid and arachidonic acid in plasma and red blood cells;
- High-sensitivity C-reactive protein.

Low-density lipoprotein cholesterol will be directly measured in patients with triglycerides > 400 mg/dl. For the other patients it will be calculated.

A fasting lipid panel including serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, calculated non-high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and total cholesterol: high-density lipoprotein cholesterol ratio will be measured at Analysis Visits 5 (Month 12), 7 (Month 24), 9 (Month 36), 11 (Month 48), and 13 (Month 60 or end of study).

The lipid biomarkers apolipoprotein B-100 and apolipoprotein C-III will be measured at Analysis Visit 5 (Month 12) and 13 (Month 60 or end of study). The fatty acids eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, and arachidonic acid for both plasma and red blood cells will be measured at Analysis Visit 5 (Month 12) and at early termination visit if it occurs before Analysis Visit 5 (Month 12). High-sensitivity C-reactive protein will be measured at end of treatment.

### 3.4 Safety variables

The safety variables that will be analyzed in the study are the following:

- AEs that are considered serious, lead to discontinuation of IP or result in a dose modification, new onset diabetes mellitus ([Section 3.4.3](#)), TIA, PHL cases or bleeding-related events ([Section 3.4.2](#))
- Laboratory tests as hematology and serum chemistry ([Section 3.4.4](#))
- Physical examinations ([Section 3.4.7](#)) and vital signs ([Section 3.4.5](#));
- Urine pregnancy test ([Section 3.4.4](#));
- Overdoses ([Section 3.4.8](#)).

#### 3.4.1 Adverse Events

In this study, only AEs that are considered serious, lead to discontinuation of IP or result in a dose modification, overdose, new onset of diabetes mellitus, TIA, PHL cases or bleeding-related events will be captured starting after randomization through the final visit.

SAEs will be recorded at all visits for the patients who prematurely discontinue IP. Non serious AEs will be collected until the final visit but no more than 30 days after the last dose of IP.

### **3.4.1.1 Severity**

Severity is classified as mild, moderate and severe. A missing severity will be classified as severe in summary tables by severity. If a patient reports the same AE more than once within that system organ class (SOC) and preferred term (PT), the AE with the worst case severity will be used in the corresponding severity summaries.

### **3.4.1.2 Relationship to study medications**

Relationship, as indicated by the Investigator, is classified as “not related”, “suspected” and “related”. AEs reported by investigator as "suspected" or "related" to study medication are categorized as “related” for AE analyses. AEs with a missing relationship will be regarded as “related” to study medication. If a patient reports the same AE more than once within that SOC and PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

### **3.4.1.3 AEs leading to discontinuation of IP**

AEs leading to discontinuation of IP will be identified if the “action taken with study treatment” is “drug withdrawal” from eCRF AE page.

### **3.4.1.4 TIAs**

TIAs are those AEs with preferred term=“ TRANSIENT ISCHAEMIC ATTACK”.

### **3.4.1.5 AEs leading to dose reduction**

AEs leading to dose reduction will be identified if the “action taken with study treatment” is “dose reduced” from eCRF AE page.

### **3.4.1.6 AEs leading to IP interruption**

AEs leading to IP interruption will be identified if the “action taken with study treatment” is “drug interrupted” from eCRF AE page.

### **3.4.1.7 SAE**

SAEs are those events recorded as “yes” to the question of “serious event” on the AE page of eCRF.

Events that are related to the primary efficacy outcomes will not be reported as SAEs, including all cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalization for unstable angina, or events associated with emergent/elective emergent/elective coronary revascularization procedure.

### **3.4.1.8 Missing dates for AEs**

For AEs with a missing or partially missing onset date the following rules apply.

- If only the day part of the AE onset date is missing and occurs in the same month and year as the date of randomization, the date of randomization will be used as the

onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE.

- If the day and month parts of the AE onset date are missing and occur in the same year as the date of randomization, the date of randomization will be used as the onset date of the AE. Otherwise, January 1 will be used to complete the onset date of the AE.
- If the AE onset date is completely missing, the date of randomization will be used as the onset date of the AE.

For AEs with a missing or partially missing end date the following rules apply.

- If only the day part of the AE end date is missing and occurs in the same month and year as the date of last contact, the date of last contact will be used as the AE end date. Otherwise, the last day of the month will be used to complete the AE end date.
- If the day and month parts of the AE end date are missing and occur in the same year as the date of last contact, the date of last contact will be used as the AE end date. Otherwise, December 31 will be used to complete the AE end date.
- If the AE end date is completely missing, the date of last contact will be used as the AE end date.

Missing or partially missing onset date or end date will be imputed only for analysis purpose but will remain as missing or partially missing in patient listings.

### **3.4.2 Bleedings**

The investigator will report any blood loss in the eCRF and the bleedings will be classified according to the thrombolysis in myocardial infarction (TIMI) non-coronary artery bypass graft bleeding definitions (Mehran et al. 2011): major, minor, requiring medical attention or minimal.

#### **Major**

-Any intracranial bleeding (excluding microhemorrhages)

-Clinically overt signs of hemorrhage associated with a drop in hemoglobin of  $\geq 5$  g/dL (0.78 mmol/L)

-Fatal bleeding (bleeding that directly results in death within 7 days)

#### **Minor**

-Clinically overt (including imaging), resulting in hemoglobin drop of 3 to  $<5$  g/dL

### **Requiring medical attention**

-Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above

-Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)

-Leading to or prolonging hospitalization

-Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

### **Minimal**

-Any overt bleeding event that does not meet any criteria above.

The bleeds are categorized into the classifications programmatically. The rule set for these classifications based on the data within the Bleed eCRF form can be found in [Appendix 4](#). If the available data are not enough to determine the TIMI bleed classification, the bleeding event will be reported as “Bleeding event not categorizable due to missing data”. A summary of bleeds location will be included to allow a better evaluation of uncategorized events.

### **3.4.3 New onset of diabetes mellitus during the study**

New onset of diabetes mellitus during the study is identified programmatically among patients without HbA1c  $\geq 6.5\%$  (48 mmol/mol) at the last measurement on or before the first dose of study medication and without medical history or AE with start date before the first dose of study medication indicating diabetes. The preferred terms to be used are those included in the *SMQ Hyperglycaemia/new onset diabetes mellitus (narrow scope)*.

New onset of diabetes mellitus during the study is identified according to at least one of the following criteria

- AE with start date on or after the first dose of study medication and indicating diabetes. The preferred terms to be used are those included in the *SMQ Hyperglycaemia/new onset diabetes mellitus (narrow scope)*
- Two consecutive values of fasting plasma glucose of  $\geq 7\text{mM}$  (126 mg/dL) on or after the first dose of study medication
- Two consecutive values of HbA1c  $\geq 6.5\%$  (48 mmol/mol) on or after the first dose of study medication

If more than one of the above criteria are met, the earliest date among the onset date of the earliest AE indicating diabetes, the date of the earliest fasting plasma glucose of  $\geq 7\text{mM}$  (126



mg/dL) confirmed by a consecutive result and the date of the earliest HbA1c  $\geq 6.5\%$  (48 mmol/mol) confirmed by a consecutive result will be considered as the onset date of the event of new onset of diabetes mellitus.

MedDRA dictionary 22.1 and corresponding SMQ will be used.

#### **3.4.4 Laboratory tests**

Laboratory tests include hematology, serum chemistry, urine pregnancy data, refer to [Appendix 2](#).

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorized as low, normal or high.

If a laboratory test is reported as above or below the limit of quantification (i.e., result includes operator  $>$ ,  $\geq$ ,  $<$ , or  $\leq$ ), the limit of quantification will be used for analysis. The result with the operator will be reported in listings.

Urine pregnancy tests, conducted only on women of childbearing potential, will be collected only once during Screening and will be analyzed by the site and recorded in the eCRF.

#### **3.4.5 Vital signs**

Height (cm) is measured only once at Visit 1.

The following measurements will be collected at multiple clinic visits:

- Sitting systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg)

There will be 3 blood pressure measurements, to be taken after at least 3 minutes of seated rest. The 1st measurement will be ignored. The average of the last 2 measurements will be collected through eCRF and will be presented in summary tables.

- Sitting heart rate (beats/minute)
- Waist circumference (cm)
- Weight (kg).

#### **3.4.6 Electrocardiogram (ECG)**

A 12-lead ECG will be performed after patient has been supine at rest for at least 5 minutes at Visit 2. Any clinically significant finding observed at Visit 2 will be included in the Medical History.

The following baseline ECG parameters will be captured.

- Heart rate (beats/minute)

- PQ interval (msec)
- RR interval (msec)
- QRS interval (msec)
- QT interval with Bazett's correction (msec)
- Clinical significance: normal, clinically non-significant abnormal and clinically significant abnormal.

### **3.4.7 Physical examination**

A physical examination consisting of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems will be performed at Visit 1 and Visits 5 as well as on Visit 13/end-of-treatment/ET.

The results of the Physical Examinations are not collected separately. Any clinically significant finding observed up to and including Visit 2 will be considered Medical History. Any new or worsened clinically significant finding observed after Visit 2 through Visit 13/EOT/ET will be considered an adverse event.

### **3.4.8 Overdoses**

A dose of more than 8 g of IP (>8 capsules) during one day should be considered as an overdose and must be reported as a SAE. Overdoses will be identified using the appropriate flag "Occurred with overdose" in the eCRF "Adverse Events" form.

## **3.5 Additional variables**

### **3.5.1 Demographic and other baseline characteristics**

The following demographic and patient baseline characteristics will be reported for this study:

- Age (years) = (date of randomization - date of birth+1)/365.25, rounded down to the nearest integer;
- Sex: male and female;
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islanders, White, and Others;
- Ethnicity (US residents only): Hispanic or Latino, not Hispanic or Latino, Not Reported, and Unknown;
- Established cardiovascular disease at baseline:
  - Yes: patients that meet 1 or more of the atherosclerotic cardiovascular disease criteria as defined in Inclusion Criteria 3a;

- No: patient that do not meet any of the Inclusion Criteria 3a.
- Region: Asia, Australia & New Zealand, Europe, Latin America and North America.

### **3.5.2 Medical history**

Medical history conditions are defined as those conditions which stopped on or prior to the date of randomization at Visit 2, or were ongoing at the time of randomization.

### **3.5.3 Prior and concomitant medications**

Prior medications are those medications taken by the patient during the 4 weeks before Visit 1 or during Screening and stopped on or prior to the date of randomization at Visit 2.

Concomitant medications are medications, other than IP, that were ongoing at the date of randomization at Visit 2 or started or stopped by the patient after the date of randomization at Visit 2. If it is not possible to define the medication to be prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

#### **3.5.3.1 Missing dates for medications**

For medications with a missing or partially missing start date the following rules apply.

- If only the day part of the medication start date is missing and occurs in the same month and year as the date of randomization, the date of randomization will be used as the start date of the medication. Otherwise, the first day of the month will be used to complete the start date of the medication.
- If the day and month parts of the medication start date are missing and occur in the same year as the date of randomization, the date of randomization will be used as the start date of the medication. Otherwise, January 1 will be used to complete the start date of the medication.
- If the medication start date is completely missing, the date of randomization will be used as the start date of the medication.

For medications with a missing or partially missing end date the following rules apply.

- If only the day part of the medication end date is missing and occurs in the same month and year as the date of last study contact, the date of last study contact will be used as the end date of the medication. Otherwise, the last day of the month will be used to complete the end date of the medication.
- If the day and month parts of the medication end date are missing and occur in the same year as the date of last study contact, the date of last study contact

will be used as the end date of the medication. Otherwise, December 31 will be used to complete the end date of the medication.

- If the medication end date is completely missing, the medication will be assumed as ongoing.

The end date should remain null for medications that are ongoing.

### **3.5.4 Duration of exposure**

Duration of exposure to study medication will be based on the first and last dose date:

- Duration of exposure (months) = (date of last dose – date of first dose + 1 day)/30.4375.

Date of first dose will be taken from the first “start date of study medication” from eCRF “Exposure” form. Date of last dose will be the latest of the “date of last dose” from eCRF “Disposition – Treatment” form or the “end date of study medication” from eCRF “Exposure” form. Intermittent missed doses will not be taken into consideration.

An additional summary will be produced that will account for interruptions.

For this summary, duration of exposure will be based on the first and last dose date for each period without treatment interruption:

Duration of exposure (months) =  $\sum(\text{end date of study medication} - \text{start date of study medication} + 1)/30.4375$

The “start/end date of study medication” for each period without treatment interruption will be taken from eCRF “Exposure” form.

### **3.5.5 Treatment compliance**

Study medications will be administered in a double-blinded fashion, 4 grams once daily. If the patient has intolerability symptoms with study drug dose of 4 g/day, a dose reduction may be required. A temporary stop of study treatment may be necessary if symptoms persist despite dose reduction.

Derivation of compliance will be based on the number of capsules dispensed and returned as reported in the eCRF “Drug Accountability” form and on the prescribed dose as collected in the eCRF “Exposure” form.

Compliance will be calculated as the number of capsules taken divided by the prescribed number of capsules that were expected to be taken considering interruptions and dose reductions. This value is expressed as a percentage on per-patient basis first, then summarized overall.

The number of capsules taken is derived as the total number dispensed – total returned.

The prescribed number of capsules is the number that would have been taken, considering interruptions and dose reductions. For patients with no treatment interruption and no dose reduction, the prescribed number of capsules is derived as (last dose date – first dose date + 1 day) x 4 capsules per day.

In case of treatment interruption, any day of treatment interruption will be subtracted from the difference (last dose date – first dose date + 1 day). Since as per CSP only temporary interruptions which last 7 or more sequential days should be reported, shorter interruptions are missed and will not be considered in this compliance algorithm. For this reason, underestimates of compliance might be possible.

In case of dose reduction, the period between first dose date and last dose date + 1 day will be fragmented in multiple segments each with a corresponding prescribed dose. Dose reduction start date will be the day of dose reduction as collected in the eCRF “Exposure” form. Dose reduction end date will be the date of the following change in prescribed dose as collected in the eCRF “Exposure” form. If there are no further change in prescribed dose, then the last dose prescribed will be considered as prescribed until end of treatment.

Once defined the start and stop date of each segment, the prescribed number of capsules for each segment is derived as (stop date of segment – start date of segment) x number of capsules per day as prescribed in the segment. The prescribed number of capsules is derived as the sum of the prescribed dose at each segment.

Study medications will be dispensed in bottles; each bottle contains 60 capsules, unless noted otherwise. Only full bottles will be dispensed each time.

### **3.5.6 End-of-Study (EOS) assessment**

Patients who discontinue IP but agree to participate with any follow-up assessments (visit or telephone) will undergo the ET visit, and the 3-week Follow-up visit for discontinuation from an SAE if applicable and brought in for an EOS visit at study completion. Unless otherwise specified, EOS assessment is defined as the last non-missing measurement for an event of interest, after baseline but on or prior to the latest of ET visit or EOS visit (including unscheduled assessments).

## **3.6 Study Completers**

To properly describe the completeness of follow-up of primary outcome measure, the following completer categories are defined:

- Patients with complete follow-up of primary outcome measure (i.e. first MACE event)  
This category includes all patients considered as under complete observation for primary outcome measure collection. This includes all patients except those who discontinued the study prior to observing a MACE event for other reasons than death or study terminated by sponsor.

- Patients with complete follow-up of total MACE events (first and subsequent MACE events)

This category includes all patients considered as under complete observation for total MACE events. This is a subset of category 1 excluding patients dying during the study and patients who discontinued the study at any time during the study except those who discontinued the study due to the study being terminated by the sponsor.

- Patients who complete study schedule

This category includes all patients completing their EOT visit at their planned Month 60 visit prior to the date of early study termination by the sponsor..

Patients with premature IP discontinuation who have consented to follow-up only through medical records will be considered as under observation for endpoint collection but are not considered as having completed study schedule.

## **4. ANALYSIS METHODS**

### **4.1 General principles**

For qualitative variables, the population size (N for sample size and n for number of patients with available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, unless otherwise stated, including n, mean, standard deviation, Q1, median, Q3, minimum, and maximum values as appropriate. Median will be presented in conjunction with Q1 and Q3. Categorical variables will be summarized as the number of patients and percentages. All summaries will be based on all randomized patients apart from safety summaries that will be based on all patients who had taken at least one dose of IP; hence missing values will also be reported as a separate level. Unless noted otherwise, percentages will be based on the count of patients with missing and non-missing values, and will be presented as 0 in case of zero counts. Extra measurements (such as unscheduled or repeated assessments) will not be included in the descriptive statistics, unless otherwise specified, but will be included in patient listings.

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. P-values will be presented with 3 decimal places. P-values will be presented as <0.001 if less than 0.001 or >0.999 if greater than 0.999 before rounding. No multiplicity adjustments will be made to the confidence intervals as they will be interpreted descriptively and used as measures of precision.

All summaries and analyses will be conducted using at least SAS® 9.4.

#### **4.1.1 Study Periods**

The following periods are defined in the study:

- Screening period: This period starts on Screening Visit 1 date and ends prior to the start of treatment period.
- Treatment period: This period starts on date of randomization and ends on the EOT visit either at Month 60 or at study closure. For patients who permanently discontinue IP before study has ended and decide not to participate with any follow-up assessments this period ends at the ET visit.
- Follow-up period: This period is defined for those patients who undergo early permanent IP discontinuation due to a SAE and starts after the EOT/ET visit and ends 3 weeks after Visit 14 (Follow-Up visit for SAE).

#### 4.1.2 Visit Window and retests

Summary tables will be presented by analysis visit ([Table 3](#)) defined based on the number of days from randomization.

The following conventions will apply:

- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All scheduled and unscheduled visit data have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.
- Data collected after the first dose of IP and up to the date of the last dose of IP + 10 days will be considered on-treatment.
- For visit based summaries
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date should be summarized, or the later, in the event the values are equidistant from the target visit day. In the event that two or more values are located on the same side of the target day at the same date and time and are the closest to the target day, the mean of the values should be summarized. Note: in summaries of extreme values all on-treatment post baseline values collected are used including those collected at unscheduled visits regardless of whether the value is closest to the target visit day.
  - Analysis visits will be defined based on the planned schedule for each parameter as defined in [Table 3](#).

For laboratory assessments, the date of sample collection rather than the date of the visit will be considered.

**Table 3 Analysis Visits by Visit Window**

<b>Analysis Visit</b>	<b>Nominal day</b>	<b>Lower bound (day)</b>	<b>Upper bound (day)</b>
<b>Plasma and Red Blood Cells Fatty Acids</b>			
Baseline	1		
Month 12	360	2	Last study day
<b>Special Lipid Markers</b>			
Baseline	1		
Month 12	360	2	1080
Month 60	1800	1081	Last study day
<b>Liver Function Tests, Lipid Panel, HBA1c, Fasting Plasma Glucose, Hematocrit, Hemoglobin, Height, Weight, Waist Circumference</b>			
Baseline	1		
Month 12	360	2	540
Month 24	720	541	900
Month 36	1080	901	1260
Month 48	1440	1261	1620
Month 60	1800	1621	Last study day
<b>Creatinine, Creatine Kinase, Glomerular Filtration Rate</b>			
Baseline	1		
Month 12	360	2	Last study day
<b>high-sensitivity C-Reactive Protein</b>			
Baseline	1		
Month 60	1800	2	Last study day
<b>Diastolic and Systolic Blood Pressure, Heart Rate</b>			
Baseline	1		
Month 3	90	2	135
Month 6	180	136	270
Month 12	360	271	450
Month 18	540	451	630
Month 24	720	631	810
Month 30	900	811	990
Month 36	1080	991	1170
Month 42	1260	1171	1350
Month 48	1440	1351	1530
Month 54	1620	1531	1710



Month 60	1800	1711	Last study day
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Due to the early termination of the study, and that safety laboratory assessments are presented for on and off treatment, many patients will be off treatment at their final visit. As many of these values will be affected due to a study level decision, these visits will be analyzed separately to the visit windows with the visit name “Study terminated by sponsor” to minimize the impact of the study termination on the presentation of the safety laboratories (hematology and serum chemistry).

#### 4.1.3 Common calculations

For quantitative measurements, change from baseline to “Time X” will be calculated as:

- Test Value at Time X – Baseline Value.

Percent change from baseline to “Time X” will be calculated as:

- $(\text{Test Value at Time X} - \text{Baseline Value}) / \text{Baseline Value} \times 100\%$ .

If baseline is not available, the change from baseline and percent change from baseline will not be calculated and will remain missing.

#### 4.1.4 Imputation rules and missing data

Date of last dose will be the latest of the “date of last dose” from eCRF “Disposition – Treatment” form or the “end date of study medication” from eCRF “Exposure” form.

For doses with missing or partially missing start or stop dates the following algorithm will be applied starting from the imputation of missing or partially missing date of start of first dose and date of stop of last dose.

The first dose start date will be imputed according to the following rules:

- If only the day part of the start date is missing and occurs in the same month and year as the date of randomization, the date of randomization will be used as the start date of the dose. Otherwise, the first day of the month will be used to complete the start date of the dose.
- If the start date is completely missing, the date of randomization will be used as the start date of the dose.

The last dose stop date will be imputed according to the following rules:

- If only the day part of the end date is missing and occurs in the same month and year as the earliest of the date of the informed consent to continue participation in the trial after permanent IP discontinuation and last study contact, the earliest of the date of the informed consent to continue participation in the trial after permanent IP

discontinuation and last study contact will be used as the end date of the dose. Otherwise, the last day of the month will be used to complete the end date of the dose.

- If the end date is completely missing, the earliest of the date of the informed consent to continue participation in the trial after permanent IP discontinuation and last study contact will be used as the end date of the dose.

For all other dates of start or stop of doses missing or partially missing the imputation algorithm will start imputing the end dates and subsequently the start dates according to the following rules.

- If only the day part of the end date is missing and occurs in the same month and year as the start date of the following dose, the start date of the following dose - 1 will be used as the end date of the dose. If only the day part of the end date is missing and occurs in the same month and year as the start date of the following dose and the start date of the following dose is partial, the 14<sup>th</sup> day of the month will be used as end date of the dose. If the end date is missing, the date before the start of the consecutive dose will be used as end date of the dose. If the end date is missing and the date of the consecutive dose is partial, then the 14<sup>th</sup> day of the month and year of the consecutive dose will be used as end date of the dose. Otherwise, the last day of the month will be used to complete the end date of the dose.
- If only the day part of the start date is missing and occurs in the same month and year as the end date of the previous dose (also considering imputed dates), the end date of the previous dose + 1 will be used as the start date of the dose. Otherwise, the first day of the month will be used to complete the start date of the dose.
- If both the stop date and the start date of consecutive doses are missing, then the stop date will be imputed to fall half way between the start date of the same dose and the stop date of the following dose. If an even number of days exists between the start date of the same dose and the stop date of the following dose, then the stop date will be taken as the midpoint value minus 1 day.

Missing or partially missing dose date will be imputed only for analysis purpose but will remain as missing or partially missing in patient listings.

For deaths with a missing or partially missing date the following rules apply.

- If only the day part of the death date is missing and occurs in the same month and year as the date of last contact, the date of last contact will be used as the death date. Otherwise, the first day of the month will be used to complete the death date.
- If the day and month parts of the death date are missing and occur in the same year as the date of last contact, the date of last contact will be used as the death date. Otherwise, January 1 will be used to complete the death date.

- If the death date is completely missing, the date of last contact will be used as the death date.

For all other efficacy events (i.e. myocardial infarction, stroke, emergent/elective coronary revascularization, hospitalization for unstable angina, atrial fibrillation, heart failure) with a missing or partially missing date of onset the following rules apply.

- If only the day part of the onset date is missing and occurs in the same month and year as the date of randomization, the date of randomization will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
- If the day and month parts of the onset date are missing and occur in the same year as the date of randomization, the date of randomization will be used as the onset date. Otherwise, January 1 will be used to complete the onset date.
- If the onset date is completely missing, the date of randomization will be used as the onset date.

For bleeding events with a missing or partially missing date of onset the following rules apply.

- If only the day part of the onset date is missing and occurs in the same month and year as the date of first dose, the date of first dose will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
- If the day and month parts of the onset date are missing and occur in the same year as the date of first dose, the date of first dose will be used as the onset date. Otherwise, January 1 will be used to complete the onset date.
- If the onset date is completely missing, the date of first dose will be used as the onset date.

For new onset of diabetes mellitus with a missing or partially missing date of onset the following rules apply.

- If only the day part of the onset date is missing and occurs in the same month and year as the date of first dose, the date of first dose will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
- If the day and month parts of the onset date are missing and occur in the same year as the date of first dose, the date of first dose will be used as the onset date. Otherwise, January 1 will be used to complete the onset date.
- If the onset date is completely missing, the date of first dose will be used as the onset date.

Missing or partially missing death or event dates will be imputed only for analysis purpose but will remain as missing or partially missing in patient listings.

For the analyses of the change from baseline to Analysis Visit 5 (Month 12) of all biomarkers except high-sensitivity C-reactive protein, for patients who have discontinued IP prematurely during the first year, prior to the Visit 5 (Month 12), the measurement from the ET visit will be included in the analysis as Analysis Visit 5 (Month 12) measurement, as per windowing rules specified in Section 4.1.2.

The impact of further missing data on the biomarker analyses will be assessed in a sensitivity analysis based on a multiple imputation scheme under a missing at random (MAR) missingness assumption. A measurement will be imputed for patients whose Analysis Visit 5 (Month 12) measurement is missing or off treatment, including cases where patients have never started treatment with study medication, prematurely discontinued treatment with study medication, lost to follow-up, dead prior to Analysis Visit 5 (Month 12), or cases of spurious missing measurements. For high-sensitivity C-reactive protein imputation will occur on the missing values at end of treatment rather than at Analysis Visit 5 (Month 12). Further details are provided in [Section 4.2.5](#).

For AEs with a missing or partially missing onset date or end date the rules as specified in [Section 3.4.1](#) will be applied.

For prior and concomitant medications with a missing or partially missing onset date the rules as specified in [Section 3.5.3](#) will be applied.

#### **4.1.5 Patient disposition**

The number of patients enrolled (i.e., provided signatures to the informed consent form for the study), randomized, took study medication after randomization, completed/ prematurely discontinued from the treatment with associated reasons for premature discontinuation, completed/withdrew from the study (by the categories defined in [Section 3.6](#)) with associated reasons for early withdrawal will be summarized by treatment arm and overall based on the FAS.

Additionally, the number of patients randomized by site, country and region will be summarized by treatment arm and overall based on FAS. Similarly, a summary of patients by populations will also be presented based on FAS. All disposition data will also be listed.

#### **4.1.6 Demographics and baseline characteristics**

Demographics and baseline characteristics will be summarized for FAS by treatment arm and overall. All demographics and baseline characteristics will be provided in listings.

#### **4.1.7 Medical history**

Medical history information will be presented for FAS and coded using MedDRA dictionary 22.1.

Medical history will be summarized as the number and percentage of patients by MedDRA SOC and PT, a patient will be counted only once within each SOC and PT. Medical history will be sorted by SOC in alphabetical order, and PTs will be sorted by decreasing frequency by the total number of patients within each SOC.

#### **4.1.8 Prior and concomitant medications**

Medications will be presented for FAS and coded using version WHODD-WHOGLOBAL\_201909\_B3 of World Health Organization Drug Dictionary (WHO-DD).

Medications will be summarized as the number and percentage of patients by World Health Organization (WHO) class name and PT; a patient will be counted only once within each WHO class name and PT. Medications will be sorted by WHO class name in alphabetical order, and PTs will be sorted by decreasing frequency of the total number of patients within each WHO class name. Separate summaries will be provided for prior medications and concomitant medications. Concomitant medications will be presented by allowed and disallowed medications. Disallowed medications are defined in Section 7.4 of CSP.

#### **4.1.9 Duration of exposure**

Duration of exposure to study medication, in months, will be presented for SAF. Summary statistics for duration of exposure will be presented by treatment arm. All data about administration of IP will be provided in a listing.

#### **4.1.10 Treatment compliance**

Treatment compliance will be presented descriptively for SAF. A sensitivity analysis will be performed setting equal to 0 all the derived compliance that are calculated to be negative and are due to data issues in the drug accountability data that can't be resolved before the database lock. In addition, overall compliance rate will be summarized as the number and percentages of patients by treatment arm with categories of "<80%", ">= 80% -- <120%" and ">=120%".

### **4.2 Analysis of efficacy outcome measures**

Unless otherwise specified, efficacy analyses will be based on FAS, using events adjudicated by CEC. The analysis for all TTE endpoints will be performed using the Cox proportional hazards model. The HR, 95% CI for HR and Wald test p-value comparing the treatment arms of Epanova versus placebo (corn oil) will be presented. Kaplan-Meier (KM) estimates for all TTE endpoints will be calculated and plotted. All data collected for the primary outcome measure, key secondary, other secondary, and tertiary outcome measures will be presented in listings.

#### **4.2.1 Primary efficacy**

The primary outcome measure is time in months from randomization to first occurrence of any component of the composite of MACE events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization

for unstable angina). The primary outcome will be analyzed based on FAS using adjudicated events.

Time-to-event analysis will be implemented using a Cox proportional hazards model (refer to [Appendix 3.1.A](#)). The proportional factor of the hazard will be modelled as a function of treatment (Epanova vs. placebo), established cardiovascular disease at baseline (yes/no), and region. A patient will be included in the established cardiovascular disease group if they satisfy Inclusion criteria 3a alone or in conjunction with primary prevention criteria (Inclusion criteria 3b and/or 3c), otherwise they will be considered without established cardiovascular disease at baselines. Region will be defined as in [Appendix 1](#) as a categorical variable.

The HR, 95% CI for HR, and Wald test p-value comparing the treatment arms of Epanova versus placebo will be presented. The event rate will be estimated as the ratio between the number of events and the time at risk in patient-years and will be presented as events per 100 patient-years at risk.

KM product-limit method (refer to [Appendix 3.1.F](#)) will be used to illustrate event probabilities in the treatment arms. The cumulative number of patients with an event, the number at risk, the Kaplan-Meier event probability, and a 95% CI for the event probability will be provided at 3-month intervals for the first year and every 6 months thereafter. The difference in cumulative incidence and corresponding number needed to treat (NNT; defined as the inverse of that difference) will be presented.

KM estimates of the cumulative proportion of patients with events will be calculated and plotted per treatment group, with the number of patients at risk indicated below the plot at specific time points. In addition, all KM curves will be truncated at a time just prior to when <10% of the randomized population is in the risk set in both groups for the primary analysis.

#### **4.2.1.1 Model Diagnostics**

A Cox-Snell residual plot will be provided to help assess the overall model fit (refer to [Appendix 3.1.C](#)).

The Cox-model relies on the assumption of a proportional hazard for the treatment effect and the other covariates included in the model. To investigate the reasonability of this assumption assessments will be performed. Results will be discussed in the light of these results.

To assess the assumption of proportional hazards the following will be provided:

- A plot of Schoenfeld residuals will be provided for the treatment effect. This plot will include a locally smoothed curve which will be added to the plot of Schoenfeld residuals to better assess any apparent trend. A flat line around 0 indicates that the model covariate does not vary over time and the proportional hazard assumptions holds for that covariate (refer to [Appendix 3.1.D](#)).
- A Log cumulative hazard plot will be provided for the treatment effect. This will be performed by plotting the Log of the negative log of the KM survival function

estimates against the log of survival time. This will be visually inspected to assess the proportionality assumption.

- These checks will be performed for the treatment effect but also for the other covariates included in the model: established cardiovascular disease at baseline (yes/no) and region.

#### **4.2.1.2 Sensitivity analysis of primary outcome measure**

To assess the validity of the assumption of proportional hazards, a sensitivity analysis will be performed including a time dependent covariate (adding a treatment-by-time interaction term) and testing for treatment effect heterogeneity over time (not under Type I error control), to assess the extent to which this represents random variation. The treatment-by-time interaction term will consider time as a categorical variable for each year. The time-dependent HRs for each 1 year of follow-up with 95% confidence bands will be tabulated and plotted in a forest plot. If a lack of proportionality is evident, the HR from the primary analysis can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves.

#### **4.2.1.3 Censoring rules for all outcome measures and vital status**

For the analysis of the primary and all key secondary endpoints, except for the analyses of time to cardiovascular death and time to all-cause death, patients will be censored at the earliest of withdrawal of consent date and last study contact. Complete endpoint information will be pursued with every effort for all patients regardless of their study medication status, unless they exercise their right to withdraw consent. Patients who have a non-fatal event will continue study follow-up. Any event observed after the earliest of withdrawal of consent date and last study contact will not be included in the analysis.

Last study contact is defined as the latest of the dates of assessments contributing to an opportunity to assess as to whether the patient has had every component of the endpoint being analyzed.

The dates of assessments that will be used include, but are not limited to,

- Date of randomization
- Start and end dates of dosing
- Date of collection of laboratory evaluations
- Date of vital sign testing
- Date of physical examinations
- Date of ECG
- Start and end dates of concomitant medications
- Start and end dates of hospitalization
- Start and end dates of AE
- Start and end dates of bleeding event
- Date of event (if not endpoint of interest)

- Date of telephone communication with patient or a designated third party on behalf of the patient, such as hospital or immediate family
- Date of end of treatment visit or early termination visit
- Date of consent withdrawn
- Date of death (if not endpoint of interest and if not reported on vital status form only)

If the last contact date is partially missing or missing, this partially missing or missing date will be imputed to the earliest possible date. The imputed last contact date should not be earlier than any of the dates considered in the derivation of the last contact.

Because data on vital status (dead or alive) is consistently pursued for all patients, including those potentially lost to follow up or withdrawn from the study, the analysis of time to all-cause death will utilize data which extends even beyond last study contact and withdrawal of consent date. For the analysis of time to all-cause death, patients who have not had the event in question will be censored at the latest of the date of last study contact and last date known to be alive.

All deaths, including those recorded at the time of vital status assessment, will be adjudicated. Because undetermined deaths will be assumed to be cardiovascular, the analysis of time to cardiovascular death as a single outcome measure will utilize data which extends beyond last study contact and withdrawal of consent date. For the analysis of time to cardiovascular death, patients will be censored at the latest of the date of last study contact, last date known to be alive, and date of non-cardiovascular death.

### **Censoring in China**

As Human Genetic Resources (HGR) approval in China was lost on 31st January 2020 it is only possible to capture an extremely limited amount of data for patients at Chinese sites after this date. Investigators will only be able to enter event data, SAE data and vital status information.

Due to this limitation there is the possibility that events prior to January 31st will fall after last contact date when defined as above. Therefore, if using the definition above the last contact date falls before January 31st 2020, but there is no evidence that a patient has left the study prior to that date, then January 31st 2020 will be set as last contact date. A patient has evidence of leaving the study if there is a study disposition date of completion or discontinuation, or a performed Visit 13/EOS/ET date before 31st January 2020.

The number of events in each component that contribute to each of the composite endpoints will be presented. To assess the impact of the above censoring rule, particularly due to possible censored events in China, the number of events in each component that would have contributed to each of the composite endpoints if there was no censoring will also be presented.



#### 4.2.1.4 Subgroup analyses of the primary outcome measure

Subgroup analyses will be performed to evaluate variation of treatment effect, as well as a test of interaction with treatment for each subgroup variable. Subgroup analyses for the following variables will be performed, and their corresponding subgroup categories are defined in [Appendix 1](#):

- age,
- diabetes at baseline (yes/no),
- sex,
- race group (Asian, Black, Caucasian and Other),
- BMI at baseline,
- Region,
- established cardiovascular disease at baseline (yes for patients that meet 1 or more of the atherosclerotic CVD criteria as defined in Inclusion Criteria 3a/no otherwise),
- high-intensity statin vs other statin treatment at baseline,
- Ezetimibe treatment at baseline,
- baseline estimated GFR,
- baseline high-sensitivity C-reactive protein,
- baseline non-high-density lipoprotein cholesterol,
- baseline triglycerides,
- baseline very low-density lipoprotein,
- baseline apolipoprotein C-III.

For all subgroup analyses, apart from those performed on the subgroups of Region and established cardiovascular disease at baseline, the proportional factor of the hazard in the Cox model will be modelled as a function of treatment (Epanova vs. placebo), established cardiovascular disease at baseline (yes/no), Region, level for the subgroup of interest and treatment by the subgroup of interest interaction.

For the subgroup analysis performed by Region, the proportional factor of the hazard will be modelled as a function of treatment, established cardiovascular disease status at baseline, Region and treatment by Region interaction.

For the subgroup analysis performed by established cardiovascular disease status at baseline, the proportional factor of the hazard will be modelled as a function of treatment, Region, established cardiovascular disease status at baseline and treatment by established cardiovascular disease status at baseline interaction.

In addition to the result tabulation described in [Section 4.2.1](#), the p-value of the interaction test will be presented, and forest plots displaying hazard ratio and 95% confidence interval for the comparisons of Epanova vs. placebo for each subgroup will be presented. P-values will be unadjusted for multiple comparisons and will be regarded as descriptive only.

A permutation-based approach will be applied for assessing the expected variability of observed effect in subgroups under an assumption of effect homogeneity. This approach simulates N number of study replicates under the assumption of effect homogeneity and is based on the SEAMOS method described in Dane et al. 2019. This will guide interpretation of subgroup results by putting the subgroup effects in context. Specifically, it provides a comparison with the extreme subgroup results that are expected under the null hypothesis of treatment homogeneity.

Each simulated study replicate is derived through a random permutation of the rows of the matrix containing subgroup factors as columns where a row uniquely corresponds to a patient. By permutation of the aforementioned subgroup matrix, the observed outcome and treatment allocation are retained, thereby ensuring that the overall treatment effect and correlation between subgroups are constant across replicates. For each such study replicate, the data is re-analyzed, rendering N multiple subgroup analyses. Within each study replicate, the subgroup-deviation from the overall result is calculated for each subgroup as a z-score defined as the difference between the subgroup estimate and the overall estimate, normalized with the standard error for the subgroup estimate. The overall estimate is defined as the treatment effect from the primary efficacy analysis. This renders an i-th reference distribution for the i-th ordered subgroup effect; here, the i corresponds to the ordering of the subgroups in z-score scale.

Observed z-scores, will be presented similar to a forest plot where a 90% probability interval of extreme effects is overlaid to help identify potential heterogeneous results. The probability interval is derived from the reference distributions of the most extreme subgroup effects in each replication. The lower limit is defined as the 5th percentile of the minimum z-scores, and the upper limit is defined as the 95th percentile of the maximum z-scores, from each replication.

The above approach will be implemented with N=2000.

#### **4.2.1.5 Supplemental analysis with censoring at time of decision to early terminate the study**

On January 13, 2020, based on the recommendations of the DMC meeting held on January 8, 2020, the decision to early terminate the study has been communicated to the sites. The communication included the instructions that patients should stop study medication.

In order to assess the treatment effect without any bias due to this decision, a supplemental analysis on the primary and key secondary endpoint will be performed, with a censoring date of 13 January 2020. Only events occurring on or before this date will be included in the analysis, and subjects with a censoring date after this date will be censored on the 13 January 2020.

The analyses will be performed on the primary and key secondary endpoints and with the same criteria of the main analysis. Results from the Cox proportional hazards model will be

presented. KM product-limit method will be used to illustrate event probabilities in the treatment arms.

#### 4.2.2 Secondary outcome analyses

If the primary endpoint objective is met (2-sided p-value <0.05; [Section 5](#)), the secondary outcomes will be evaluated hierarchically at an overall alpha of 0.05 for each comparison, sequentially in order to control the family wise error rate at 0.05. Once a key secondary endpoint is not met at alpha 0.05, all subsequent comparisons will be considered exploratory with nominal p-values. If the study is stopped at any time prior to the accrual of the stipulated 1,600 primary (MACE) events then the testing thresholds are detailed in [Section 5](#).

Key secondary outcome measures (tested at  $\alpha=0.05$ , conditional on success of the primary outcome) include:

1. The composite measure of MACE that include the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
2. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
3. The composite measure of cardiovascular events that include the first occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the subgroup of patients with established cardiovascular disease at baseline.
4. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina.
5. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina in the subgroup of patients with established cardiovascular disease at baseline.
6. Time to cardiovascular death.
7. Time to cardiovascular death in the subgroup of patients with established cardiovascular disease at baseline.
8. Time to all-cause death.
9. Time to all-cause death in the subgroup of patients with established cardiovascular disease at baseline.

The test of effect in the subgroup of patients with established cardiovascular disease at baseline will be performed from a model with interaction between the variables of established cardiovascular disease status at baseline and treatment in addition to the effects included in the primary analysis. The HR in the subgroup will be derived from the linear combination of the estimated effects of the treatment and interaction between treatment and established

cardiovascular disease status at baseline. This will be presented together with the 95% CI for HR and the Wald test p-value comparing the treatment arms of Epanova versus placebo in the subgroup of patients with established cardiovascular disease at baseline.

The effect of Epanova on other secondary outcome measures will also be assessed for the subgroup of patients with established cardiovascular disease at baseline but will not be under Type I error control. A Kaplan Meier Curve and the difference in cumulative incidence and corresponding NNT will be presented for the primary and key secondary outcome measures in the subgroup of patients with established cardiovascular disease at baseline.

Consistency of effect in pre-specified subgroups will be investigated within the subgroup of patients with established cardiovascular disease at baseline (for subgroups specified in [Section 4](#)). This will be done by fitting the Cox regression model with subgroup and treatment-by-subgroup effect described in [Section 4.2.1.4](#) to the data in the subgroup of patients with established cardiovascular disease at baseline. Results will be presented as described in that section.

Other secondary outcome measures (evaluated using nominal p-values; NOT part of the hierarchical testing sequence and are exploratory) include time to:

- emergent/elective coronary revascularization
- hospitalization for unstable angina
- fatal or non-fatal myocardial infarction
- non-fatal myocardial infarction
- fatal or non-fatal stroke
- non-fatal stroke.

The other secondary outcome measures will be analyzed the same as outlined above for the primary outcome measures in [Section 4.2.1](#).

#### **4.2.3 Tertiary outcome analyses**

The tertiary outcome measures will include:

- Time to first occurrence of new onset atrial fibrillation.
- Time to first occurrence of the composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systemic thromboembolism including arterial stent thrombosis (except coronary) or venous thromboembolism, i.e. deep vein thrombosis and/or pulmonary embolism.
- Time to first occurrence of a heart failure event.
- Second, third, fourth, and total number occurrences of major cardiovascular events (primary and key secondary outcome measures).

- The time to first CV-related hospitalization.

Time to tertiary outcome measures will be analyzed the same as outlined above for the primary outcome measure in [Section 4.2.1](#). The analysis of the tertiary outcomes will be considered observational only.

For the time to first occurrence of the composite measure of total thrombotic events the analysis will include all the venous thromboembolisms, pulmonary embolism and confirmed stent thrombosis collected in the eCRF “Tertiary Endpoints” form and all the AEs identified using the PTs as reported in [Appendix 5](#).

Exploratory analysis of the occurrence of all events occurring within patients during follow-up (i.e., first and subsequent events), will be made for the primary and key secondary outcome measures, ie MACE events, cardiovascular events and coronary events. In these analyses, events occurring on the same date will be counted as one event and non-fatal events occurring on the same date as cardiovascular/coronary death will be counted as a cardiovascular/coronary death. The analyses will use the same censoring rules as in the primary outcome analyses. Bar plots showing the distribution of number of events per patient will also be presented.

The Nelson-Aalen estimator of the mean cumulative function will be used to illustrate the average cumulative number of events per patient over the study follow-up time per treatment arm (Nelson 2003).

The average number of events during follow-up will be modelled using Negative binomial regression using the log link function with log follow-up time as offset and including treatment, established cardiovascular disease status at baseline, and region as covariates. Rate ratios (RRs) and 95% CIs for the RRs comparing event rates between the treatment arms will be calculated. The Negative binomial regression models will be implemented using the SAS GENMOD procedure.

In addition, Cox proportional hazards models modified for the analysis of recurrent events will be used to model time until an event, in models including treatment, established cardiovascular disease status at baseline, and region.

The Andersen-Gill Cox model, which applies a counting process formulation of follow-up time, will be used to estimate HRs for events by treatment arms (Anderson and Gill 1982).

The Wei-Lin-Weissfeld Cox regression model, modified for the analysis of recurring and terminal events by Li and Lagakos (Wei and Lin 1989, Li and Lagakos 1997, Scenario II), will be used to estimate HRs for the 1st, 2nd, 3rd, and 4th event.

Both the Andersen-Gill and Wei-Lin-Weissfeld Cox models will utilize robust sandwich estimator for the regression coefficient standard errors, to adjust for dependencies between event times within the same individual (Lin and Wei 1989). Both Cox models will be implemented using the SAS PHREG procedure.

To account for informative censoring from death, joint frailty models will be used to estimate HRs for recurring events. This analysis will be carried out for MACE events, cardiovascular events and coronary events. Estimation will be based on the %JointFrailty SAS macro (Toenges and Jahn-Eimermacher 2020). The model will assume a gamma distributed frailty term and a Weibull baseline hazard functions. The estimation of the model will be based on the Probability Integral Transformation (PIT) method. Adaptive Gaussian quadrature will be applied as superior to non-adaptive quadrature when associated with the PIT method (Toenges and Jahn-Eimermacher 2020). The NLMIXED procedure selects the appropriate number of quadrature points based on the evaluation of the log likelihood at the starting values of the parameters.

Additional sensitivity analyses for the total event analysis include descriptive analyses of IP discontinuations after time at event (i.e. number and percentages of patients with first, second and third event), analyses counting all events including those occurring on the same date and analyses of Cox models with and without robust standard errors.

#### **4.2.4 Exploratory outcome measures**

The primary outcome measure will be repeated for on-treatment MACE events using FAS, where on-treatment MACE events are defined as the first occurrence of MACE components that started on or after the date of first dose of study medication and on or prior to the permanent discontinuation of study medication + 10 days. Patients who do not have an event that satisfies this criterion will be censored on the earliest between date of permanent discontinuation of study medication +11 days and the censoring date or the randomization date if the patient never started study medication.

An exploratory analysis of time to first occurrence of fatal myocardial infarction and sudden cardiac death will be performed. The exploratory outcome measure will be analyzed as outlined above for the primary outcome measure in [Section 4.2.1](#). The analysis will be considered observational only.

#### **4.2.5 Biomarkers Efficacy**

The analysis of biomarkers, except for high-sensitivity C-reactive protein, will focus on the differences between Epanova versus placebo (corn oil) in the Analysis Visit 5 (Month 12) measurement expressed as a percentage of the baseline measurement. High-sensitivity C-reactive protein will be analyzed similarly but for the end of treatment measurement in place of the Analysis Visit 5 (month 12) measurement. This analysis will assess the effect of IP on biomarkers, and hence only data from samples collected up to the date of the last dose of IP + 10 days will be included in the analysis.

The following fasting lipid biomarkers will be included in the analysis: serum triglycerides, total cholesterol, low-density lipoprotein cholesterol (in patients with triglycerides > 400 mg/dl low-density lipoprotein cholesterol will be directly measured), high-density lipoprotein cholesterol, calculated non-high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and total cholesterol: high-density lipoprotein cholesterol ratio.

The following additional fasting biomarkers will be included in the analysis: apolipoprotein B-100, apolipoprotein C-III, eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, and arachidonic acid for both plasma and red blood cells and high-sensitivity C-reactive protein.

Analysis of covariance (refer to [Appendix 3.2.A](#)) will be used to model percent change from baseline as a function of treatment group as a main effect and baseline as a covariate.

The dependent variable will be the natural log of the Analysis Visit 5 (Month 12) measurement expressed as a % of the baseline measurement, i.e.  $\ln\left(100 \cdot \frac{y_{12}}{y_0}\right)$ , where  $y_{12}$  and  $y_0$  are the measurements at Analysis Visit 5 (Month 12) (or end of treatment for high-sensitivity C-reactive protein) and baseline, respectively. This transform will be applied to improve the normality of residuals. The measurement at baseline in logarithmic scale will be used as covariate in addition to the treatment group.

LSMeans, the difference in LSMean between the two treatment arms and, 95% CIs will be provided on the back-transformed scale. LSMean and difference in LSMean on the back-transformed scale are estimates for Geometric Means and Geometric Mean Ratios respectively. P-values will be also provided from the ANCOVA model. The model will be implemented using SAS® PROC GLM.

For patients who have discontinued IP prematurely during the first year, prior to Analysis Visit 5 (Month 12), the result for the assessment done at the Early Termination (ET) visit will be carried forward to Analysis Visit 5 (Month 12) and will be included in the analysis in place of the missing measurement at Analysis Visit 5 (Month 12).

In addition, for quantitative biomarkers, descriptive statistics will be presented for baseline and percent change from baseline to each post-baseline visit.

#### **4.2.5.1 Multiple Imputation scheme**

To assess the impact of further missing data on the effect of Epanova in biomarker parameters, a sensitivity analysis will be performed. The sensitivity analysis will be based on a Multiple Imputation scheme under a MAR missingness assumption.

The sensitivity analysis will assess the treatment effect of Epanova on biomarker parameters in the hypothetical situation that the patients had continued with treatment and had their Analysis Visit 5 (Month 12) measurement as planned.

Hence, a measurement will be imputed for patients whose Analysis Visit 5 (Month 12) measurement are missing or off treatment, including cases where patients have never started treatment with study drug, prematurely discontinued treatment with study drug, lost to follow-up, dead prior to the Analysis Visit 5 (Month 12), or cases of spurious missing measurements.

For patients with missing data at the Analysis Visit 5 (Month 12), data will be imputed in a multiple imputation scheme in a two-step fashion for each biomarker variable:

Step 1: The imputation scheme will impute missing values from a model with parameters  $(\beta^*, \sigma^*)$  where  $(\beta^*, \sigma^*)$  are drawn from the posterior distribution of the parameters  $(\hat{\beta}, \hat{\sigma})$  from a regression model of the existing Analysis Visit 5 (Month 12) measurements (O'Kelly and Ratitch 2014).  $\beta$  represents the regression effects and  $\sigma$  the covariance. This regression model will have the natural logarithm of the Analysis Visit 5 (Month 12) measurements as the dependent variable. Explanatory variables will be treatment and the natural logarithm of the baseline value. In addition, the dichotomous variable for any occurrence of SAE or MACE event during the first year from randomization will be added as an effect thought to explain the missingness mechanism. The seed for this imputation will be 3275.

Note: Step 1 will result in M datasets without missing values at Analysis Visit 5 (Month 12) for patients with a non-missing baseline value, except for patients who had both baseline and Analysis Visit 5 (Month 12) measurement missing. These patients will not have had any imputed measurements.

Step2: The ANCOVA modelled, as described for the biomarker analysis, is performed for each of the M datasets. This will result in M estimates of the LS means and LS mean differences.

Finally, the M LS-mean and LS-mean differences are pooled according to Rubin's Rules. This will be performed in SAS using PROC MIANALYZE (O'Kelly and Ratitch 2014).

The above description of the MAR sensitivity analysis using Multiple Imputation will be implemented with M=1000 imputations.

This sensitivity analysis will be performed for all biomarker variables and will thus be modified for high-sensitivity C-reactive protein to impute missing values at end of treatment rather than at Analysis Visit 5 (Month 12).

### **4.3 Analysis of safety outcome measures**

All outputs for safety outcomes will be based on SAF.

Exposure to study medications, AEs/SAEs, bleedings, new onset of diabetes mellitus during the study, clinical laboratory data and vital signs will be summarized per treatment arm using descriptive statistics.

Subgroup analyses will be performed on SAEs, AEs leading to discontinuation of IP, new onsets of diabetes mellitus during the study and bleedings. Subgroup analyses for the following variables will be performed. Their corresponding subgroup categories are defined in [Appendix 1](#).

- age,
- sex,
- race group,
- Region,



- established cardiovascular disease at baseline (yes for patients that meet 1 or more of the atherosclerotic CVD criteria as defined in Inclusion Criteria 3a/no otherwise).

#### 4.3.1 AEs

AEs will be coded using MedDRA dictionary 22.1.

AE summaries will only include AEs with onset date on or after the day of first dose of study medication. Non-serious AEs with onset date more than 30 days after the last dose of study medication will not be included. All SAEs will be included.

- Overall summaries of AEs will include the following categories: any AE, any AE with outcome of death, any SAE, any AE related to study medication, any AE leading to discontinuation of IP, dose reduction or dose interruption.
- Incidence of AEs will be presented by SOC and PT, also broken down further by maximum severity, relationship to study medications, AEs leading to discontinuation of IP; AEs with outcome of death and SAE.
- Both a separate summary of on-treatment AEs and on-treatment SAEs will be provided, i.e. with onset up to the date of the last dose of IP + 10 days.

The event rate per 100 patient years at risk will be included in these summaries, where the event rate per 100 patient years at risk is calculated as:

$$\frac{\text{total number of patients with at least one event}}{\text{total number of patient years at risk}} * 100$$

The total number of patients at risk is calculated as the sum of [(date of last dose +10 days)- date of first dose+1]/365.25

- All AE data will be presented in AE listings. Selected AE data will be listed for AEs with outcome of death, AEs leading to discontinuation of IP, dose reduction or dose interruption, TIAs and SAEs.
- Safety in the subgroup of patients with established cardiovascular disease at baseline will be assessed by a tabulation of SAEs by SOC and PT by treatment group for subgroup of patients with established cardiovascular disease at baseline in the SAF.
- Incidence of SAEs and AEs leading to discontinuation of IP, overall and broken down by severity, will be presented by age category, sex, race group and Region. Separate tables by age category, sex, race group and Region will be presented on the subgroup of patients with established cardiovascular disease at baseline.

### 4.3.2 Bleedings

Bleedings will not be adjudicated by CEC. Bleedings as collected in the eCRF “Bleed” form will be included in the analysis.

The bleedings will be classified according to the thrombolysis in myocardial infarction (TIMI) non-coronary artery bypass graft bleeding definitions (Mehran et al. 2011): major, minor, requiring medical attention or minimal.

Only bleeding events with an onset on or after the first dose of study medication will be included in analyses.

Time from first dose to first bleeding will be computed as  $TTE \text{ (months)} = (\text{date of event} - \text{date of first dose} + 1 \text{ day}) / 30.4375$

Time from first dose to first bleeding will be presented by a Kaplan-Meier summary and figure.

Patients will be censored in this TTE analysis at last date of potential assessment for bleeds, defined as latest of:

- Start and End Dates of AE
- Start and End Dates of Dosing
- Date of Hemoglobin or Hematocrit Lab Results
- Start and End Date of Hospitalization
- Recorded Scheduled Visit

If the last date of potential assessment for bleeds is partially missing or missing, this partially missing or missing date will be imputed to the earliest possible date (as outlined in Section 4.1.4).

Bleedings events will be also presented in listings and tabulations by treatment arm and SOC/PT, per TIMI bleeding category.

In addition, location of the bleeding events will be presented in listings and tabulated by treatment arm per TIMI bleeding category.

Results will be presented overall and by age category, sex, race group and Region. Separate tables by age category, sex, race group and Region will be presented on the subgroup of patients with established cardiovascular disease at baseline.

Complete information on the programmatic bleeding determination is available in [Appendix 4](#).

### 4.3.3 New onset of diabetes mellitus during the study

Number of patients with new onset of diabetes mellitus during the study will be presented by treatment group. Only diabetes onset on or after the first dose of study medication will be included in the analysis. Results by type of diabetes onset will be also reported.

Time from first dose to first diabetes onset will be computed as TTE (months) = (date of event – date of first dose + 1 day)/30.4375

Time from first dose to first diabetes onset will be presented by a Kaplan-Meier summary and figure. The log-rank test will be applied to test treatment difference. Patients will be censored in this TTE analysis at last date of potential assessment for diabetes, defined as latest of:

- Start and End Dates of AE
- Start and End Dates of Dosing
- Date of HbA1c or Plasma Glucose Lab Results
- Start and End Date of Hospitalization
- Recorded Scheduled Visit.

If the last date of potential assessment for diabetes is partially missing or missing, this partially missing or missing date will be imputed to the earliest possible date (as outlined in Section 4.1.4).

Results will be presented overall and by age category, sex, race group and Region. Separate tables by age category, sex, race group and Region will be presented on the subgroup of patients with established cardiovascular disease at baseline.

New onset of diabetes mellitus during the study will be also presented in listings.

### 4.3.4 Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for hematology and serum chemistry. In case of a bleeding event or an AE with potential elevated liver enzymes, results from local laboratories might be collected in the eCRF in the form “Bleed” (hematocrit and hemoglobin) and “Liver Lab Values” (AST, ALT, total bilirubin and alkaline phosphatase). These values are included in the safety laboratory analyses as detailed in [Appendix 2](#). All longitudinal laboratory data will be analyzed by analysis visit as in [Table 3](#). A complete list of laboratory tests is available in [Appendix 2](#).

The following summaries and listings will be provided for laboratory data:

- Summary of baseline and change from baseline by visit (for quantitative measurements in hematology (hematocrit and HbA1c), serum chemistry (except alkaline

phosphatase), lipid data, special lipid markers, Plasma and red blood cells Fatty Acids).

- Shifts from baseline to post-baseline by visit (based on assessments relative to normal range in hematology (hematocrit and HbA1c), serum chemistry (except alkaline phosphatase), lipid data, special lipid markers, Plasma and red blood cells Fatty Acids).
- A listing of patients who potentially met Hy's laws criteria (ALT or AST  $\geq 3$ xULN and total bilirubin (BILI)  $\geq 2$ xULN elevation, and in which the elevation in transaminases precedes or is on the same day as the elevation in BILI.) on or after the first dose of study medication will be presented by treatment group for Safety analysis set. Figures displaying maximum total bilirubin on or after the first dose of study medication against maximum ALT and AST on or after the first dose of study medication will also be produced.
- Number and percentage of patients meeting predefined criteria for marked abnormalities at any time during treatment will be provided. A laboratory value is considered a marked abnormality (MA) if it is outside the pre-defined criteria for marked abnormality ([Table 4](#)). If both the baseline and on-treatment values of a parameter are beyond the same MA limit for the parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low MA limit, and the post-baseline value is beyond the high MA limit (or vice-versa), then the post-baseline value will be considered a MA.
- For a patient with at least 1 abnormal assessment meeting predefined criteria for marked abnormalities, all values for those laboratory tests with at least one abnormal assessment will be listed.
- Urine pregnancy tests, conducted only on women of childbearing potential, will be collected only once during Screening and will be analyzed by the site. All pregnancy test data will be listed.

**Table 4**                      **Marked abnormality criteria**

<b>Clinical laboratory variables</b>	<b>Units</b>	<b>Low</b>	<b>High</b>
<b><u>CLINICAL CHEMISTRY</u></b>			
<b><u>(Serum or Plasma)</u></b>			
Alanine Aminotransferase (ALT)	U/L		>3X ULN >5X ULN >10X ULN >20X ULN
Aspartate Aminotransferase (AST)	U/L		>3X ULN >5X ULN >10X ULN >20X ULN
Bilirubin, Total	mg/dL		> 2X ULN if PreRx > ULN; > 3X ULN if PreRx > ULN
Creatinine	mg/dL		Absolute Value >2.5 mg/dL (221 µmol/L)
Fasting blood glucose (Plasma)	mg/dL	<50 mg/dL (<2.8 mmol/L)	> 350 mg/dL (>19.4mmol/L)
Creatine Kinase	U/L		>5X ULN

#### **4.3.5 ECG**

Any clinically significant ECG findings observed at Visit 2 will be included in the Medical History.

#### **4.3.6 Vital signs**

A summary table of baseline and change from baseline will be provided for SBP, DBP and heart rate, waist circumference and weight. All vital sign data will be provided in listings.

#### **4.3.7 Physical examination**

Any clinically significant finding observed up to and including Visit 2 will be reported under Medical History. Any new or worsened clinically significant finding observed after Visits 2 through Visit 13/EOS/ET will be reported in the AE panel.

No separate summary tables or listings will be provided for physical examination data.

#### **4.3.8 Overdoses**

Overdoses will be listed along with key patient information. Time from start of treatment to overdose (days), time from last dose prior to overdose start date (days)", outcome and action taken (with IP) will be also reported.

### **5. INTERIM ANALYSES**

Accrual of a total of 1,600 5-point MACE (primary efficacy) events is required to have approximately 90% power for this study (refer to [Section 1.4](#)). The study is designed to continue until this number of events has accrued. However, 2 interim analyses of the primary endpoint are planned and the study may be recommended for termination by the DMC early if the stopping rule for superiority or futility is met. The Executive Steering Committee and the Sponsor will decide whether or not to enforce the DMC's recommendation.

A group sequential design will be used to preserve the overall type I error probability of 0.05.

Planned interim analyses on 5-point MACE will be performed around the time when 50% (800) of adjudicated MACEs have occurred, and again when 75% (1,200) of adjudicated MACEs have occurred. The final analysis is scheduled when at least 1,600 adjudicated MACEs have occurred. The group sequential superiority boundaries (absolute value of z-score) for the 1st and 2nd interim analyses are 3.719. Boundaries (absolute value of z-score) for futility at the 1st and 2nd interim look are 0.3085 and 1.2375, respectively. The significance threshold (z-score) for the final analysis is 1.9602, which correspond to a nominal p-value of 0.025. CI for the main Primary analysis on MACE will be constructed at the 95% level. All thresholds are constructed accounting for DMC recommendations for stopping for efficacy are "non-binding" in the sense of necessary but not sufficient.

Superiority boundaries are defined based on Haybittle-Peto rule. Specifically, this uses a 1-sided p-value threshold held constant at 0.0001 for each look prior to final. The final comparison will be carried out at a 2-sided alpha of 0.05. Futility boundaries are based on Lan-DeMets alpha spending function that approximates an O'Brien-Fleming boundary in the setting of this particular study. Details on the thresholds for stopping can be seen in [Table 5](#). Corresponding thresholds in the hazard-ratio and the p-value scales are also presented. If the study is stopped for either futility or superiority patients will be brought in for their final visit and assessed for further events.

**Table 5 Interim Analysis Plan**

Interim analysis	Number of adjudicated Events (%)	Approximate Time from FPFV (months) <sup>a</sup>	Boundaries (z-scale) <sup>b</sup>	
			Superiority	Futility
1	800 (50%)	32	$abs(z_{obs}) > 3,719$	$abs(z_{obs}) < 0,3085$
			$HR^c < 0,7682$	$HR^c > 0,9785$
			$p < 0,0002^d$	$p > 0,7578^d$
2	1,200 (75%)	43	$abs(z_{obs}) > 3,719$	$abs(z_{obs}) < 1,2375$
			$HR^c < 0,8063$	$HR^c > 0,9312$
			$p < 0,0002^d$	$p > 0,216^d$
Final	1,600 (100%)	54	$abs(z_{obs}) > 1,9602$	
			$HR < 0,9064$	
			$p < 0,05$	
FPFV = First Patient First Visit; abs = absolute value. <sup>a</sup> Based on simulations of 10000 trials <sup>b</sup> Non-binding boundaries <sup>c</sup> HR = hazard ratio <sup>d</sup> 2-sided				

## 6. CHANGES OF ANALYSIS FROM PROTOCOL

Only the following documented changes are made at the time analysis.

- For consistency purpose with other Epanova studies, FAS is used in this SAP interchangeably with the notation of intent-to-treat population from the protocol. The definition of these 2 populations remains the same for the study.
- To show treatment effect in the specific subgroup of patients with established cardiovascular disease at baseline over both primary and key secondary efficacy outcome measures, analyses of these outcome measures in this subgroup have been added to the hierarchical testing sequence found in [Sections 1.1.3, 3.3.4 and 4.2.2.](#)

- The second, third, fourth, and total number occurrences of major cardiovascular events (primary and secondary outcome measures) and the time to first CV-related hospitalization have been added as tertiary outcomes for completeness of analysis.
- The CSP includes as covariate in the Cox proportional hazards model for the time to event analysis the multiple risk factors without established cardiovascular disease at baseline. However due to constraints on the data collection this ordering of patients is not applicable. Hence, this covariate which characterizes only the patients without established cardiovascular disease at baseline has been removed from the model.
- In this SAP, the analysis of on-treatment MACE events is not referred as a sensitivity analysis, since it does not assess the impact of deviations from model assumptions on results, but instead answers another research question. It has therefore presented as an analysis on exploratory outcome measure.
- The CSP states that “the analysis of biomarkers (e.g. lipids or other biomarkers) will be based on the differences in change from baseline (Month 0) to Month 12 (primarily), between placebo (corn oil) and Epanova treatments.”. As high-sensitivity C-reactive protein is not recorded at Month 12, but only at end of treatment, the planned analysis of difference from baseline to Month 12 is not possible for this parameter. Hence, the analysis will focus on the difference from baseline to end of treatment.

An MMRM analysis is stated as the planned approach to assess the impact of treatment on biomarker parameters. However, the biomarkers are not repeatedly measured between Baseline and Month 12. It is only by including measurements after Month 12 that it could be an MMRM analysis model. If missingness will mainly be monotone, the patients with missing values at month 12 will also have missing data at all subsequent visits. Thus, the analysis will be only based on the patients with values at Month 12, which will only provide an unbiased estimate under MCAR missingness. Because of these issues, the analysis model has been changed from MMRM to ANCOVA, for all biomarker variables.

As it is indicated in the CSP that missingness may not be under MCAR but under MAR and that this will be investigated, a sensitivity analysis utilizing MI under MAR assumption will be added.

It has been more clearly stated that this analysis will be performed “on-treatment” and therefore that measurements after premature discontinuation of study medication will not be included.

This SAP also specifies the type of transformation that will be applied to the biomarker measure. Based on assessment on data from previous trials, it was deemed that the natural log of  $100 + \% \text{ change from baseline}$  would be sufficient to meet the normality assumption.

- This SAP clarifies that the bleeding classifications are not directly collected on the Bleed eCRF form and therefore all bleeds will have to be categorized into the classifications programmatically. The rule set for these classifications based on the data within the Bleed eCRF form have been specified in [Appendix 4](#). In this section



the SAP clarifies that also hematocrit values will be considered along with hemoglobin values.

- In this SAP time to all-cause death has been changed into a key secondary measure, along with the corresponding subgroup analysis on patients with established cardiovascular disease at baseline.
- Due to the decision to early terminate the study, a supplemental analysis has been added to assess any bias on the primary and key secondary endpoints caused by data collected after this decision being communicated to the sites.

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## 8. APPENDICES

### APPENDIX 1 SUBGROUPS AND GEOGRAPHIC REGIONS

Age at baseline (years)	<65,
	≥65 to ≤75
	>75
Sex	Female
	Male
Race group	Asian
	Black
	Caucasian
	Other
BMI (kg/m <sup>2</sup> )	<30
	≥ 30
Region	Country
Asia	CHINA (MAINLAND)
	JAPAN
	SOUTH KOREA
	TAIWAN
Australia & New Zealand	SOUTH AFRICA
	AUSTRALIA
	NEW ZEALAND
Europe	BELGIUM
	CZECH REP
	DENMARK
	ESTONIA
	HUNGARY
	ITALY
	LITHUANIA
	NETHERLANDS
	POLAND
	RUSSIA
	UK
	UKRAINE
Latin America	MEXICO
North America	CANADA
	USA
Diabetes at baseline	Yes (patients with history of diabetes mellitus at baseline or with baseline HbA1c >=

	6.5% (48 mmol/mol))
	No (patients without history of diabetes mellitus at baseline and without baseline HbA1c $\geq$ 6.5% (48 mmol/mol))
Established cardiovascular disease at baseline	Yes (patients that meet 1 or more of the atherosclerotic CVD criteria as defined in Inclusion Criteria 3a)
	No (patients that do not meet any of the atherosclerotic CVD criteria as defined in Inclusion Criteria 3a)
High-intensity statin	Yes (patients with an ongoing treatment with rosuvastatin $\geq$ 20 mg or atorvastatin $\geq$ 40 mg once daily at the randomization visit.)
	No (patients without an ongoing treatment with rosuvastatin $\geq$ 20 mg or atorvastatin $\geq$ 40 mg once daily at the randomization visit.)
Ezetimibe treatment	Yes (patients with an ongoing treatment with Ezetimibe at the randomization visit.)
	No (patients without an ongoing treatment with Ezetimibe at the randomization visit.)
Baseline estimated GFR	$<60$ mL/min/1.73 m <sup>2</sup>
	$\geq 60$ mL/min/1.73 m <sup>2</sup>
Baseline high-sensitivity C-reactive protein	$<0.2$ mg/dL ( $<2$ mg/L)
	$\geq 0.2$ mg/dL ( $\geq 2$ mg/L)
Baseline non-high-density lipoprotein cholesterol	$<3.62$ mmol/L ( $<140$ mg/dL)
	$\geq 3.62$ mmol/L ( $\geq 140$ mg/dL)
	$<3.387$ mmol/L ( $<300$

Baseline triglycerides	mg/dL)
	$\geq 3.387$ mmol/L ( $\geq 300$ mg/dL)
Baseline very low-density lipoprotein	<P25
	$\geq P25$ and <P50
	$\geq P50$ and <P75
	$\geq P75$
Baseline apolipoprotein C III	<P25
	$\geq P25$ and <P50
	$\geq P50$ and <P75
	$\geq P75$

## APPENDIX 2 LIST OF LABORATORY TESTS

Category	Laboratory Tests
Hematology	Hematocrit
	Hemoglobin A1c (Hb A1c)
	Hemoglobin*
Serum Chemistry	Creatine Kinase
	Alanine Aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Total and Direct Bilirubin
	Creatinine
	Alkaline phosphatase (ALP)**
	Glomerular Filtration Rate (GFR)
	high-sensitivity C-reactive protein
	Plasma Glucose
Pregnancy Test	Urine Pregnancy Test
Lipid Panel	Triglycerides
	Total cholesterol
	Low-density lipoprotein cholesterol
	High-density lipoprotein cholesterol
	non-high-density lipoprotein cholesterol
	Very low-density lipoprotein cholesterol
	Total cholesterol: high-density lipoprotein cholesterol ratio
Special Lipid Markers	Apolipoprotein B-100
	Apolipoprotein C-III
Plasma and red blood cells Fatty Acids	Eicosapentaenoic acid
	Docosahexaenoic acid
	Docosapentaenoic acid
	Arachidonic acid
* Hemoglobin values are collected on eCRF Bleeds form only and are analyzed by local laboratories. They will be included in the algorithm to classify bleeding events and will be listed, but not included in the summary statistics of laboratory evaluations.	
** Alkaline phosphatase values are collected on eCRF Liver Lab form only and are analyzed by local laboratories. They will be included in the analysis to identify Hy's Law cases and will be listed, but not included in the summary statistics of laboratory evaluations.	

## APPENDIX 3 STATISTICAL MODELS

### Appendix 3.1 Cox proportional hazard model, Kaplan-Meier (KM) product-limit method, event rates and hazard plots

#### A. Model description

The Cox proportional hazard model is given by

$$h(t) = h_0(t) \cdot \exp(X\beta),$$

where  $h(t)$  is the hazard function at time  $t$ ;  $h_0(t)$  is the baseline hazard function,  $X$  is the vector of explanatory variables and  $\beta$  is vector of regression parameters to be estimated.

The hazard ratio, 95% CI for the hazard ratio, and Wald test p-value comparing the treatment arms of Epanova versus placebo (corn oil) will be presented.

#### B. Implementation

The Cox proportional hazards model will be implemented in SAS, PROC PHREG. Ties will be handled using Breslow's method, which is the default setting in PROC PHREG.

#### C. Cox-Snell residuals

Cox-Snell residuals will be used to assess the overall fit of the Cox proportional hazard model as proposed by Kay (1977) who applied the methods in Cox and Snell (1968) to derive the residuals for the proportional hazards regression model.

Suppose a proportional hazards model

$$h(t) = h_0(t) \cdot \exp(X\beta),$$

where  $h(t)$  is the hazard function at time  $t$ ;  $h_0(t)$  is the baseline hazard function,  $X$  is the vector of explanatory variables and  $\beta$  is vector of regression parameters to be estimated.

The Cox-Snell residual for the  $j$ -th observation is defined as:

$$r_j = \hat{H}_0(T_j) \exp\left(\sum_{k=1}^p b_k x_{jk}\right), j = 1, \dots, n.$$

Where  $\mathbf{b} = (b_1, \dots, b_p)$  are the maximum likelihood estimates of  $\beta$  from the postulated model,  $\hat{H}_0(t)$  is the Breslow's estimate of baseline cumulative hazard function at time  $t$  and  $T_j$  is the observed death time for subject  $j$ .

If the model is correct and the  $\mathbf{b}$ 's are close to the true values of  $\beta$  then the  $r_j$  should look like a censored sample from a unit exponential distribution.

To check whether the  $r_j$ 's behave as a sample from a unit exponential, we compute the Nelson-Aalen estimator of the cumulative hazard rate of the  $r_j$ 's. If the unit exponential fits the data then this estimator should be approximately equal to the cumulative hazard rate of the unit exponential  $H_E(t) = t$ . Thus, a plot of the estimated cumulative hazard rate of

the  $\mathbf{r}_j$ 's,  $\mathbf{H}_r(\mathbf{r}_j)$  versus  $\mathbf{r}_j$  should be a straight line through the origin (Klein and Moeschberger 1997). Any large departure means that the model is lack of fit otherwise the model is adequate.

D. Plot of Schöenfeld residuals (Grambsch and Therneau 1994)

The Cox proportional hazards model is assuming the hazard functions are proportional and remained constant over time between treatment arms and other covariates included in the model. A popular method for evaluating the proportional hazards assumption is to examine the Schöenfeld residuals. Grambsch and Therneau (1994) show that a scaled version of the Schöenfeld residuals at time  $k$  for a particular covariate  $p$  will approximate the change in the regression coefficient at time  $k$ :

$$E(\mathbf{S}_{kp}) + \widehat{\beta}_p \approx \beta_j(t_k)$$

Where  $\mathbf{S}_{kp}$  is the scaled Schöenfeld residual for covariate  $p$  at time  $k$ ;  $\beta_p$  is the time-invariant coefficient, and  $\beta_j(t_k)$  is the time-variant coefficient. In other words, the mean of Schöenfeld residual for coefficient  $\beta_p$  at time  $k$  estimates the changes in the coefficient at time  $k$ . Thus, if the mean is 0 across the time that suggests the coefficient  $\beta_p$  does not vary over time and the proportional hazards assumptions holds for covariate  $p$ .

Considering the relationship with time may not be linear, so time will be transformed onto logarithm scale. Visual inspection of the Schöenfeld residual plot will be made to see if the mean value of Schöenfeld residuals departs from 0. This plot will include a locally smoothed curve which will be added to the plot of Schoenfeld to better assess any apparent trend. Departure from 0 indicates the coefficient varies from time and the proportional hazards assumption does not hold.

E. Test of Treatment-by-time interaction terms

Treatment-by-time interaction term will be included into the model to test if the treatment effect of Epanova is time-dependent. A statistically significant interaction indicates the assumption of proportional hazards between the 2 treatment arms does not hold. If a departure from the proportional hazards assumption is detected then this analysis will also serve as a sensitivity analysis of the primary treatment effect.

F. Model description

The KM estimator is a nonparametric estimator of the survival function  $\mathbf{S}(t)$ :

$$\widehat{\mathbf{S}}(t) = \prod_{t_j \leq t} \mathbf{1} - \frac{d_j}{n_j}$$

where  $d_j$  is the number of individuals who experience the event at time  $t_j$  and  $n_j$  is the number of individuals who have not yet experienced the event at time  $t_j$  and are therefore still at risk.

G. Log-cumulative hazard plots

Log-cumulative hazard plots will be created by plotting the log of the negative log of the KM survival function estimates against the log of the survival time. A visual inspection will



be made using the log-cumulative hazard plots method to see if the proportional hazards assumption between the two treatment arms is appropriate. Under proportional hazard assumption the lines should be approximately parallel with constant vertical separation.

#### H. Event Rates

Event rates at specific times (e.g. yearly, etc.) will be expressed as the number of patients who have had an event divided by the exposure (in e.g. patient-years) of those at risk of having the same type of event.

### Appendix 3.2 Analysis of covariance model

#### A. Model description

The analysis of covariance (ANCOVA) model is given by

$$\mathbf{y}_i = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}_i,$$

where  $\mathbf{y}_i$  is the outcome score for the  $i$ th patient,  $\mathbf{X}$  is the vector of explanatory variables,  $\boldsymbol{\beta}$  is vector of regression parameters to be estimated and  $\mathbf{e}_i$  is the residual for the  $i$ th patient, assumed to be normally distributed with mean zero.

The LS Means are computed as  $\mathbf{L} * \boldsymbol{\beta}$  where  $\mathbf{L}$  is the hypothesis matrix,  $\boldsymbol{\beta}$  is defined as  $\mathbf{g}inv(\mathbf{X}'\mathbf{X}) * \mathbf{X}'\mathbf{Y}$ .

The hypothesis matrix  $\mathbf{L}$  is composed by row vectors each corresponding to a single hypothesis.

The row vector of the least square mean for a given effect has all the  $\mathbf{L}_i$  corresponding to continuous covariates set to their mean value, the  $\mathbf{L}_i$  corresponding to the given level of the effect of interest equal to 1, the  $\mathbf{L}_i$  corresponding to other levels of the effect of interest equal to 0, and all  $\mathbf{L}_i$  corresponding to other categorical effects equal to  $\frac{1}{j}$ , where  $j$  is the number of levels of each effect.

The standard error of  $\mathbf{L} * \boldsymbol{\beta}$  is defined as  $\sqrt{\mathbf{L} * \mathbf{g}inv(\mathbf{X}'\mathbf{X}) * \mathbf{L}' * \sigma^2}$ , where  $\mathbf{g}inv$  is the generalized inverse and the variance of residuals  $\sigma^2$  is estimated by the mean square error.

## APPENDIX 4 TIMI BLEED CLASSIFICATIONS DERIVATION

### Major:

At least one of:

- Any intracranial bleeding (excluding microhemorrhages)

Defined as Location = “INTRACRANIAL” or “SUBDURAL HEMATOMA”

- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of  $\geq 5$  g/dL (0.78 mmol/L)

Defined as

- a) The difference between prior hemoglobin and any hemoglobin record associated with the bleeding event is  $\geq 50$  [prior to transfusion] (The SI unit for hemoglobin is g/L, so after applying the conversion factor the criteria becomes  $\geq 50$  g/L) or the difference between prior hematocrit and any hematocrit record associated with the bleeding event is  $\geq 15\%$ .

and

- b) Clinically overt signs defined as:

- CT, MRI, Ultrasound, Endoscopy or “Other Bleeding Procedure” was performed

and/or

- If one of the following is checked on the BLEED CRF fields that ask investigators to “Select all items that are relevant to this bleed”

- a) required laboratory evaluation is checked OR
- b) required surgical treatment is checked OR
- c) required transfusion is checked OR
- d) required medication change is checked OR
- e) compression or nasal packing is checked OR
- f) tamponade is checked OR
- g) drainage is checked OR
- h) hemostasis of bleeding vessel is checked

and/or

- Required a transfusion of the following type:
  - a) blood unit is checked OR
  - b) re-infuse shed blood is checked OR
  - c) platelets is checked OR

- d) FFP is checked OR
- e) R-factor VIIa is checked OR
- f) cryoprecipitate is checked OR
- g) other procoagulant factors is checked

and/or

Action Taken with Study treatment (from AE CRF) is “DOSE REDUCED” or “DRUG INTERRUPTED”.

- Fatal bleeding (bleeding that directly results in death within 7 days)

Defined as Outcome on Bleed eCRF ticked as “FATAL” and end date is within (and including) 7 days from start date.

If end date of bleed is missing assume worst case scenario that patient satisfies this criterion.

**Minor:**

- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

Same definition as in Major for Clinically overt signs (with an additional possible sign of “Required imaging to look for bleeding” is checked), however for minor bleeds hemoglobin/hematocrit drop is defined as:

- a) The difference between prior hemoglobin and any hemoglobin record associated with the bleeding event is  $\geq 30$  and  $< 50$  [prior to transfusion] (The SI unit for hemoglobin is g/L, so after applying the conversion factor the criteria becomes  $\geq 30$  and  $< 50$  g/L) or
- b) the difference between prior hematocrit and any hematocrit record associated with the bleeding event is  $\geq 10\%$  and  $< 15\%$

**Requiring medical attention:**

Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above

At least one of:

- Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)

Defined as any intervention of: "MEDICATION CHANGE", "SURGICAL OR RADIOLOGY TREATMENT" or a transfusion of any type

and/or

Action Taken with Study treatment (from AE CRF) is “DOSE REDUCED” or “DRUG INTERRUPTED”.

- Leading to or prolonging hospitalization

Defined as Hospitalization ticked as YES or there is a hospitalization date on the corresponding AE CRF for the patient

- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Defined as any evaluation by "HEALTHCARE PROFESSIONAL" has been performed.

### **Minimal:**

All other bleeding events that are not classified in any of the above categories.

If the available data are not enough to determine the hemoglobin/hematocrit drop and consequently the TIMI bleed classification, the bleeding event will be reported as “Bleeding event not categorizable due to missing data”. The location of the bleeding event as collected in the eCRF will be tabulated and listed if available to help provide additional information to those reviewing the Clinical Study Report (CSR) and manuscripts.

### **Rules for calculating Hemoglobin/Hematocrit in relation to BLEED event**

- All bleed events requiring laboratory evaluation must have a minimum of 2 entries if hemoglobin/hematocrit were evaluated. One entry must be prior to the onset of the bleeding event and the second value taken during the assessment of the event.

NOTE: The hemoglobin/hematocrit value used prior to the start of the bleed event may be taken from medical records prior to the subject’s participation in the study. The initial entry should be the most recent hemoglobin/hematocrit analysis prior to the current bleed.

- Any hemoglobin/hematocrit record associated with the bleeding event is defined as a record that occurs during the start date of the bleed to the end date of the bleed. If multiple records exist, then the record with the lowest result will be used.

The prior hemoglobin/hematocrit record is defined as the latest record prior to the bleeding event being classified that is independent of another bleed. This record can include the hemoglobin/hematocrit result from the discharge of the patient due to a previous bleed. If no hemoglobin/hematocrit result is available after the first bleeding the hemoglobin/hematocrit result prior to the previous bleed can be considered as the prior value if there is a minimum time of two months (61 days) between the events.

- If data between prior and bleed event labs is a mixture of hemoglobin and hematocrit the following rules will be utilized:
  - If prior is hemoglobin but bleed event is hematocrit then divide the

hematocrit (%) by 3 to calculate hemoglobin (g/dL) equivalent.

- If prior is hematocrit but bleed event is hemoglobin then divide the prior hematocrit (%) by 3 to calculate hemoglobin (g/dL) equivalent

If the above stated rules are not enough to compute the drop, for example where the hemoglobin/ hematocrit result during the bleed is missing or there are no the hemoglobin/ hematocrit result prior to the bleed and independent of another bleed, the drop will be assumed missing.

## APPENDIX 5 PTS FOR TERTIARY OUTCOME ANALYSIS OF TOTAL THROMBOTIC EVENTS

The PTs for tertiary outcome analysis of total thrombotic events are given in the table below from MedDRA SMQs Embolic and thrombotic events, arterial and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

From Embolic and thrombotic events, arterial (MedDRA SMQ)

Amaurosis
Amaurosis fugax
Angioplasty
Aortic embolus
Aortic thrombosis
Arterial angioplasty
Arterial bypass occlusion
Arterial bypass thrombosis
Arterial graft
Arterial stent insertion
Arterial thrombosis
Atherosclerotic plaque rupture
Blindness transient
Brachiocephalic artery occlusion
Coeliac artery occlusion
Embolia cutis medicamentosa
Embolism arterial
Femoral artery embolism
Hepatic artery embolism
Hepatic artery occlusion
Hepatic artery thrombosis
Hypothenar hammer syndrome
Iliac artery embolism
Iliac artery occlusion
Leriche syndrome
Mesenteric arterial occlusion
Mesenteric arteriosclerosis
Mesenteric artery embolism
Mesenteric artery stenosis
Mesenteric artery stent insertion
Mesenteric artery thrombosis
Ophthalmic artery thrombosis
Penile artery occlusion

Peripheral arterial occlusive disease
Peripheral arterial reocclusion
Peripheral artery angioplasty
Peripheral artery occlusion
Peripheral artery thrombosis
Peripheral embolism
Peripheral endarterectomy
Popliteal artery entrapment syndrome
Profundaplasty
Pulmonary artery occlusion
Pulmonary artery therapeutic procedure
Pulmonary artery thrombosis
Pulmonary endarterectomy
Pulmonary tumour thrombotic microangiopathy
Renal artery angioplasty
Renal artery occlusion
Renal artery thrombosis
Renal embolism
Retinal artery embolism
Retinal artery occlusion
Retinal artery thrombosis
Spinal artery embolism
Spinal artery thrombosis
Splenic artery thrombosis
Splenic embolism
Subclavian artery embolism
Subclavian artery occlusion
Subclavian artery thrombosis
Thromboembolectomy
Thrombotic microangiopathy
Thrombotic thrombocytopenic purpura
Truncus coeliacus thrombosis
Vascular pseudoaneurysm thrombosis
Visual acuity reduced transiently

From Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (MedDRA SMQ)

Administration site thrombosis
Adrenal thrombosis
Angiogram peripheral abnormal
Application site thrombosis

Arteriovenous fistula occlusion
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Artificial blood vessel occlusion
Bone infarction
Catheter site thrombosis
Choroidal infarction
Device embolisation
Device occlusion
Device related thrombosis
Embolic pneumonia
Embolism
Eye infarction
Graft thrombosis
Haemorrhagic adrenal infarction
Haemorrhagic infarction
Hepatic infarction
Hepatic vascular thrombosis
Implant site thrombosis
Incision site vessel occlusion
Infarction
Infusion site thrombosis
Injection site thrombosis
Inner ear infarction
Instillation site thrombosis
Intestinal infarction
Medical device site thrombosis
Mesenteric vascular insufficiency
Mesenteric vascular occlusion
Microembolism
Optic nerve infarction
Pancreatic infarction
Paradoxical embolism
Paraneoplastic thrombosis
Paresis
Pituitary infarction
Placental infarction
Postpartum thrombosis
Prosthetic cardiac valve thrombosis
Prosthetic vessel implantation
Renal infarct
Renal vascular thrombosis



Retinal infarction
Retinal vascular thrombosis
Shunt occlusion
Shunt thrombosis
Splenic infarction
Splenic thrombosis
Stoma site thrombosis
Surgical vascular shunt
Testicular infarction
Thrombectomy
Thromboangiitis obliterans
Thrombolysis
Thrombosis
Thrombosis in device
Thrombosis mesenteric vessel
Thyroid infarction
Tumour embolism
Tumour thrombectomy
Tumour thrombosis
Vaccination site thrombosis
Vascular access site thrombosis
Vascular device occlusion
Vascular graft occlusion
Vascular graft thrombosis
Vascular stent occlusion
Vascular stent thrombosis
Vessel puncture site occlusion
Vessel puncture site thrombosis

## APPENDIX 6      PTS FOR CARDIOVASCULAR EVENTS

The PTs for cardiovascular events are given in the table below.

Acute cardiac event
Acute Coronary Syndrome
Altered state of consciousness
Amaurosis
Amaurosis fugax
Aneurysm
Aneurysm repair
Aneurysm ruptured
Angina pectoris
Angina unstable
Anginal Equivalent
Angiogram abnormal
Angiogram cerebral abnormal
Angiogram peripheral abnormal
Angioplasty
Anomalous atrioventricular excitation
Aortic aneurysm
Aortic aneurysm repair
Aortic aneurysm rupture
Aortic arteriosclerosis
Aortic bypass
Aortic calcification
Aortic dilatation
Aortic disorder
Aortic dissection
Aortic dissection rupture
Aortic elongation
Aortic embolus
Aortic intramural haematoma
Aortic necrosis
Aortic occlusion
Aortic rupture
Aortic stenosis
Aortic stent insertion
Aortic surgery
Aortic thrombosis
Aortic valve calcification
Aortic valve disease

Aphasia
Apparent death
Apparent death
Apparent life threatening event
Arterial bypass operation
Arterial insufficiency
Arterial occlusive disease
Arterial repair
Arterial restenosis
Arterial spasm
Arterial stenosis
Arterial stent insertion
Arterial therapeutic procedure
Arterial thrombosis
Arteriogram abnormal
Arteriogram carotid abnormal
Arteriogram coronary abnormal
Arteriosclerosis coronary artery
Arteriospasm coronary
Artery dissection
Artificial heart implant
Ataxia
Atherectomy
Atherosclerotic plaque rupture
Atrial appendage closure
Atrioventricular block
Atrioventricular block complete
Atrioventricular dissociation
Balance disorder
Balint's syndrome
Basal ganglia haematoma
Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery aneurysm
Basilar artery occlusion
Basilar artery perforation
Basilar artery stenosis
Basilar artery thrombosis
Blindness transient
Blood creatine phosphokinase abnormal
Blood creatine phosphokinase increased

Blood creatine phosphokinase MB abnormal
Blood creatine phosphokinase MB increased
Brain death
Brain herniation
Brain natriuretic peptide abnormal
Brain natriuretic peptide increased
Brain oedema
Brain operation
Brain stem haemorrhage
Brain stem infarction
Brain stem ischaemia
Brain stem microhaemorrhage
Brain stem stroke
Brain stem syndrome
Brain stem thrombosis
Cardiac aneurysm repair
Cardiac arrest
Cardiac asthma
Cardiac complication associated with device
Cardiac death
Cardiac discomfort
Cardiac disorder
Cardiac dysfunction
Cardiac enzymes increased
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiac fibrillation
Cardiac index decreased
Cardiac massage
Cardiac operation
Cardiac output decreased
Cardiac perforation
Cardiac procedure complication
Cardiac stress test abnormal
Cardiac tamponade
Cardiac valve rupture
Cardiac ventricular disorder
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal

Cardiac ventriculogram right abnormal
Cardiogenic shock
Cardiomegaly
Cardiomyopathy
Cardiomyopathy acute
Cardiomyopathy alcoholic
Cardioplegia
Cardiopulmonary bypass
Cardiopulmonary failure
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Carotid aneurysm rupture
Carotid angioplasty
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery bypass
Carotid artery disease
Carotid artery dissection
Carotid artery dolichoectasia
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery perforation
Carotid artery restenosis
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Carotid revascularisation
Catheterisation cardiac abnormal
Central nervous system haemorrhage
Central venous pressure increased
Cerebral venous sinus thrombosis
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar ataxia
Cerebellar embolism
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar infarction

Cerebellar ischaemia
Cerebellar microhaemorrhage
Cerebellar syndrome
Cerebral aneurysm perforation
Cerebral arteriosclerosis
Cerebral arteriovenous malformation haemorrhagic
Cerebral arteritis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery stenosis
Cerebral artery thrombosis
Cerebral ataxia
Cerebral capillary telangiectasia
Cerebral circulatory failure
Cerebral disorder
Cerebral gas embolism
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage traumatic
Cerebral hyperperfusion syndrome
Cerebral hypoperfusion
Cerebral infarction
Cerebral ischaemia
Cerebral microangiopathy
Cerebral microembolism
Cerebral microhaemorrhage
Cerebral reperfusion injury
Cerebral revascularisation
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vascular occlusion
Cerebral vasoconstriction
Cerebral venous thrombosis
Cerebral ventricle dilatation
Cerebral ventricular rupture
Cerebrospinal thrombotic tamponade
Cerebrovascular accident
Cerebrovascular arteriovenous malformation
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular operation

Cerebrovascular spasm
Cerebrovascular stenosis
Charcot-Bouchard microaneurysms
Chest discomfort
Chest pain
Cheyne-Stokes respiration
Chronic left ventricular failure
Chronic right ventricular failure
Circulatory collapse
Coma
Complications of transplanted heart
Computerised tomogram coronary artery abnormal
Computerised tomogram head abnormal
Conduction disorder
Congestive cardiomyopathy
Consciousness fluctuating
Coordination abnormal
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Coronary angioplasty
Coronary arterial stent insertion
Coronary artery aneurysm
Coronary artery bypass
Coronary artery compression
Coronary artery dilatation
Coronary artery disease
Coronary artery dissection
Coronary artery embolism
Coronary artery insufficiency
Coronary artery occlusion
Coronary artery perforation
Coronary artery reocclusion
Coronary artery restenosis
Coronary artery stenosis
Coronary artery stent removal
Coronary artery surgery
Coronary artery thrombosis
Coronary bypass thrombosis
Coronary endarterectomy
Coronary no-reflow phenomenon
Coronary ostial stenosis

Coronary revascularisation
Cranial nerve disorder
Cranial nerve palsies multiple
Cranial nerve paralysis
Craniocerebral injury
Death
Delayed ischaemic neurological deficit
Depressed level of consciousness
Diabetic cardiomyopathy
Diastolic dysfunction
Diplegia
Dissecting coronary artery aneurysm
Disturbance in attention
Drain of cerebral subdural space
Drop attacks
Dysarthria
Dysphonia
Dyspnoea at rest
Dyspnoea exertional
Dyspnoea paroxysmal nocturnal
ECG electrically inactive area
ECG signs of myocardial ischaemia
Ejection fraction decreased
Electrocardiogram Q wave abnormal
Electrocardiogram QRS complex prolonged
Electrocardiogram QT interval abnormal
Electrocardiogram QT prolonged
Electrocardiogram repolarisation abnormality
Electrocardiogram ST segment abnormal
Electrocardiogram ST segment depression
Electrocardiogram ST segment elevation
Electrocardiogram ST-T segment abnormal
Electrocardiogram ST-T segment depression
Electrocardiogram ST-T segment elevation
Electrocardiogram T wave abnormal
Electrocardiogram U wave inversion
Electrocardiogram U wave present
Embolic cerebral infarction
Embolic stroke
Embolism
Embolism arterial
Endarterectomy



Exercise electrocardiogram abnormal
Exercise test abnormal
Facial nerve disorder
Facial paresis
Gait apraxia
Gait deviation
Gait disturbance
Gait spastic
Generalised oedema
Gerstmann's syndrome
Glabellar reflex abnormal
Graft thrombosis
Grand mal convulsion
Haemodynamic instability
Haemorrhage coronary artery
Haemorrhage intracranial
Haemorrhagic cerebral infarction
Haemorrhagic infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Heart and lung transplant
Heart transplant
Hemianopia
Hemianopia heteronymous
Hemianopia homonymous
Hemiapraxia
Hemihyperaesthesia
Hemidysaesthesia
Hemiparesis
Hemiplegia
Hemisensory neglect
Hemitaxia
Hepatojugular reflux
Hoffmann's sign
Horner's syndrome
Hydrocephalus
Hyperaesthesia
Hyperdynamic left ventricle
Hypertrophic cardiomyopathy
Hypoaesthesia
Hypogeusia
Hypoglossal nerve disorder

Hypoglossal nerve paralysis
Hypoglossal nerve paresis
Hypokinesia
Hypoperfusion
Hyporeflexia
Hyposmia
Hypovolaemic shock
IIIrd nerve disorder
IIIrd nerve paralysis
IIIrd nerve paresis
Implantable defibrillator insertion
Incoherent
Infarction
Intra-aortic balloon placement
Intracardiac pressure increased
Intracardiac thrombus
Intra-cerebral aneurysm operation
Intracerebral haematoma evacuation
Intracranial aneurysm
Intracranial artery dissection
Intracranial haematoma
Intracranial hypotension
Intracranial pressure increased
Intracranial venous sinus thrombosis
Intraoperative cerebral artery occlusion
Intrapericardial thrombosis
Intraventricular haemorrhage
Ischaemic cardiomyopathy
Ischaemic cerebral infarction
Ischaemic mitral regurgitation
Ischaemic stroke
IVth nerve disorder
IVth nerve paralysis
IVth nerve paresis
Jugular vein distension
Kounis syndrome
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Lateropulsion
Left atrial appendage occlusion
Left atrial dilatation

Left ventricular dysfunction
Left ventricular failure
Life support
Locked-in syndrome
Long QT syndrome
Loss of consciousness
Loss of proprioception
Low cardiac output syndrome
Man-in-the-barrel syndrome
Masked facies
Mechanical ventilation
Mechanical ventilation complication
Meningorrhagia
Metabolic cardiomyopathy
Microvascular coronary artery disease
Monoparesis
Monoplegia
Musculoskeletal Chest Pain
Myocardial haemorrhage
Myocardial hypoperfusion
Myocardial infarction
Myocardial ischaemia
Myocardial oedema
Myocardial reperfusion injury
Myocardial rupture
Nervous system injury
Neurological symptom
Nocturnal dyspnoea
Non-cardiac chest pain
Non-cardiogenic pulmonary oedema
N-terminal prohormone brain natriuretic peptide abnormal
N-terminal prohormone brain natriuretic peptide increased
Nystagmus
Ocular ischaemic syndrome
Oculocephalogyric reflex absent
Oculofacial paralysis
Oedema blister
Oedema due to cardiac disease
Oedema peripheral
Optic nerve infarction
Orthopnoea
Ortner's syndrome

Papillary muscle infarction
Papillary muscle rupture
Paraesthesia
Paralysis
Paralysis flaccid
Paraparesis
Paraplegia
Paresis
Paresis cranial nerve
Percutaneous coronary intervention
Pericardial disease
Pericardial effusion
Pericardial haemorrhage
Pericardial rub
Peripheral nerve paresis
Peripheral paralysis
Peripheral Swelling
Phlebectomy
Phrenic nerve paralysis
Pituitary infarction
Pleural effusion
Post procedural myocardial infarction
Post procedural stroke
Post stroke epilepsy
Post stroke seizure
Posthaemorrhagic hydrocephalus
Postinfarction angina
Precerebral artery occlusion
Prinzmetal angina
Pseudostroke
Pulmonary hilar enlargement
Pulmonary microemboli
Pulmonary oedema
Pulse absent
Pulseless electrical activity
Putamen haemorrhage
Pyramidal tract syndrome
Quadriparesis
Quadriplegia
Rales
Red blood cells CSF positive
Reperfusion arrhythmia

Respiratory arrest
Respiratory failure
Restenosis
Restrictive cardiomyopathy
Resuscitation
Reversible ischaemic neurological deficit
Right ventricular diastolic collapse
Right ventricular dysfunction
Right ventricular failure
Ruptured cerebral aneurysm
Shock
SI QIII TIII pattern
Silent myocardial infarction
Sinoatrial block
Slow response to stimuli
Slow speech
Spasmodic dysphonia
Spastic diplegia
Spastic paralysis
Spastic paraplegia
Speech disorder
Spinal artery embolism
Spinal artery thrombosis
Spinal cord haematoma
Spinal cord haemorrhage
Spinal cord herniation
Spinal cord infarction
Spinal cord ischaemia
Spinal cord paralysis
Spinal epidural haemorrhage
Spinal Stroke
Spinocerebellar disorder
Stent embolisation
Stent placement
Stress cardiomyopathy
Stress echocardiogram abnormal
Stroke in evolution
Subdural effusion
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subendocardial ischaemia

Sudden cardiac death
Sudden death
Supranuclear palsy
Thalamic infarction
Thalamus haemorrhage
Thrombectomy
Thromboembolectomy
Thrombolysis
Thrombosis
Thrombosis in device
Thrombotic cerebral infarction
Thrombotic stroke
Torsade de pointes
Transient ischaemic attack
Transmyocardial revascularisation
Trifascicular block
Trigeminal nerve disorder
Trigeminal nerve paresis
Trigeminal palsy
Troponin I increased
Troponin increased
Troponin T increased
Ultrasonic angiogram abnormal
Ultrasound Doppler abnormal
Unresponsive to stimuli
Vascular device occlusion
Vascular graft
Vascular graft occlusion
Vascular graft thrombosis
Vascular insufficiency
Vascular occlusion
Vascular stenosis
Vascular stent insertion
Vasogenic cerebral oedema
Venous pressure increased
Venous pressure jugular abnormal
Venous pressure jugular increased
Ventricular arrhythmia
Ventricular assist device insertion
Ventricular asystole
Ventricular dysfunction
Ventricular dyskinesia

Ventricular failure
Ventricular fibrillation
Ventricular hypertrophy
Ventricular remodeling
Ventricular septal defect acquired
Vertebral artery aneurysm
Vertebral artery dissection
Vertebral artery occlusion
Vertebral artery perforation
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Vertebrobasilar Stroke
Vestibular nystagmus
Vibratory sense increased
VIIth nerve paralysis
Visual field defect
Visual midline shift syndrome
Visual pathway disorder
VIth nerve disorder
VIth nerve paralysis
VIth nerve paresis
Wallenberg syndrome
Wellens' syndrome
White matter lesion
XIth nerve paralysis

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