# STATISTICAL ANALYSIS PLAN

Final Version 1.0, dated 17 June 2011

**A Randomized, Double-Blind, Placebo Controlled Multi-Center and Parallel Group Study of the Safety, Tolerability and Efficacy of YM150 in combination with Standard Treatment in Secondary Prevention of Ischemic Vascular Events in Patients with Acute Coronary Syndromes.**

**The RUBY-1 study**

ISN: 150-CL-201
EudraCT number: 2008-005972-29
Quanticate reference: Q_012\Q_00427

Astellas Pharma Europe B.V.

## Table of Contents

# I. SIGNATURES

Prepared by: Graham Wetherill Date: 17 June 2011

Graham Wetherill, MSc, CStat, CSci, ARCS
BioStatistician,Study Statistician,
Clinical Data Science
AstellasAstellas Pharma Europe B.V.

Approved by: A Garcia Date: 17 June 2011

Alberto Garcia-Hernandez, MSc
Associate Biostatistics Director,
Clinical Data Science
Astellas Pharma Europe B.V.

Richard Bucknall Date: 17-JUN-2011

Richard Bucknall BSc
Associate Clinical Research Director
Medical and Clinical Development Department
Astellas Pharma Europe B.V.

# II. LIST OF ABBREVIATIONS AND KEY TERMS

**List of Abbreviations**

| Abbreviations | Description of abbreviations |
|---|---|
| ACS | Acute Coronary Syndrome |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ASA | Acetyl Salicylic Acid |
| AST | Aspartate aminotransferase |
| bid | Twice daily administration |
| BP | Bodily pain |
| BUN | Blood Urea Nitrogen |
| CABG | Coronary Artery Bypass Graft |
| CAD | Coronary Artery Disease |
| CI | Confidence Interval |
| CK-MB | Creatine Kinase Myocardial Band |
| CRF | Case Report Form |
| CRNM | Clinically Relevant Non Major |
| CRO | Contract Research Organization |
| DBP | Diastolic Blood Pressure |
| DM2 | Diabetes mellitus type 2 |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| EOT | End of Treatment |
| EQ-5D | European Quality of Life-5 Dimensions |
| ESC | European Society of Cardiology |
| EudraCT | Clinical trial database regulated by European Community |
| FAS | Full Analysis Set |
| FXa | Factor Xa |
| GCP | Good Clinical Practice |
| γGT | Gamma-Glutamyl Transferase |
| GP | Glycoprotein |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| IAC | Independent Adjudication Committee |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISN | International Study Number |
| ISTH | International Society of Thrombosis and Hemostasis |
| LBBB | Left Bundle Branch Block |
| LDH | Lactate dehydrogenase |

| Abbreviations | Description of abbreviations |
|---|---|
| LFT | Liver Function Test |
| LMWH | Low Molecular Weight Heparin |
| MCS | Mental Health Composite Summary |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| NSAIDS | Non Steroidal Anti Inflammatory Drugs |
| NSTE | Non ST Elevation |
| NSTEMI | Non ST segment elevation myocardial infarction |
| PCI | Percutaneous Coronary Intervention |
| PCS | Physical Health Composite Summary |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PKAS | Pharmacokinetic Analysis Set |
| PPS | Per Protocol Set |
| PT | Preferred Term |
| PTM | Placebo to match tablets |
| QALY | Quality Adjusted Life Years |
| qd | Once daily administration |
| QoL | Quality of life |
| QT | Time from the beginning of the QRS complex to the end of the T wave |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SF-36 | Short-form health survey with 36 questions |
| SFL | Screening Failure Log |
| SG | Standard Gamble |
| SOP | Standard Operating Procedure |
| STE | Elevation of the ST segment on a ECG |
| STEMI | ST segment elevation myocardial infarction |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TIA | Transient Ischemic Attack |
| TIMI | Thrombolysis in Myocardial Infarction |
| UFH | Unfractionated Heparin |
| ULN | Upper Limit of Normal |
| V | Visit |
| VD | Discontinuation Visit |
| VTE | Venous Thromboembolism |
| WBC | White Blood Cell |
| YM150 | Phenylenediamide compound containing a diazepane moiety<br>The study medication |

**List of Key Terms**

| Terms | Definition of terms |
|---|---|
| Baseline | 1) Observed values/findings which are regarded as calibrated zero status in the present study.<br>2) Time when 'Baseline' is observed. |
| Clopidogrel or No Clopidogrel | Standard antiplatelet treatment with clopidogrel (with or without ASA) or ASA alone (no clopidogrel). |
| Discontinuation | The act of concluding participation, prior to completion of all protocol required elements, in a trial by an enrolled patient. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a patient (also a noun referring to such a discontinued patient); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the patient; d) sponsor-initiated discontinuation. Note that patient discontinuation does not necessarily imply exclusion of patient data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard. |
| Enroll | To register or enter into a clinical trial; transitive and intransitive.<br>Informed consent precedes enrollment, which precedes or is contemporaneous with randomization. |
| Index Event | Patient presents with NSTE-ACS or STE-ACS at the hospital for which he or she will be treated initially and will qualify for enrollment in this study. |
| Intervention | The drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study: e.g., health-related quality of life, efficacy, safety, pharmacoeconomics. |
| Investigational period | Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a patient, and continues until the last assessment after completing administration of the test drug or comparative drug. |
| Pre-investigational period | Period of time before entering the investigational period, usually from the time of starting a patient enrolling into study until just before the test drug or comparative drug (sometimes without randomization) is given to a patient. |
| Post-investigational period | Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events are done in this period. |
| Randomization | Action to allocate a patient to the treatment group or treatment cohort.<br>Depending on the type of rules for handling for study drugs, 'Randomization' is usually executed just before entering the 'investigational period'. |

| Terms | Definition of terms |
|---|---|
| RUBY-1 Modified ISTH bleeding events | This is the definition of Major, CRNM and minor bleeding events in the protocol – when setting up the adjudication process; it became apparent that the definition was not quite the same as the ISTH criteria. The definition in the protocol has been labeled "Ruby-1 modified ISTH criteria" and used as primary. The unmodified ISTH criteria are used as a secondary variable |
| Screening | 1) Process for retrieving candidates for the study.<br>2) Process for checking the eligibility of patients usually done during the "pre-investigational period". |
| Screening Failure | Screened patient, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized or open-label study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-investigational period. |
| Study period | Period of time from start to end–of-the study. |
| Patient | An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control. |
| Variable | Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values. |

# 1 INTRODUCTION

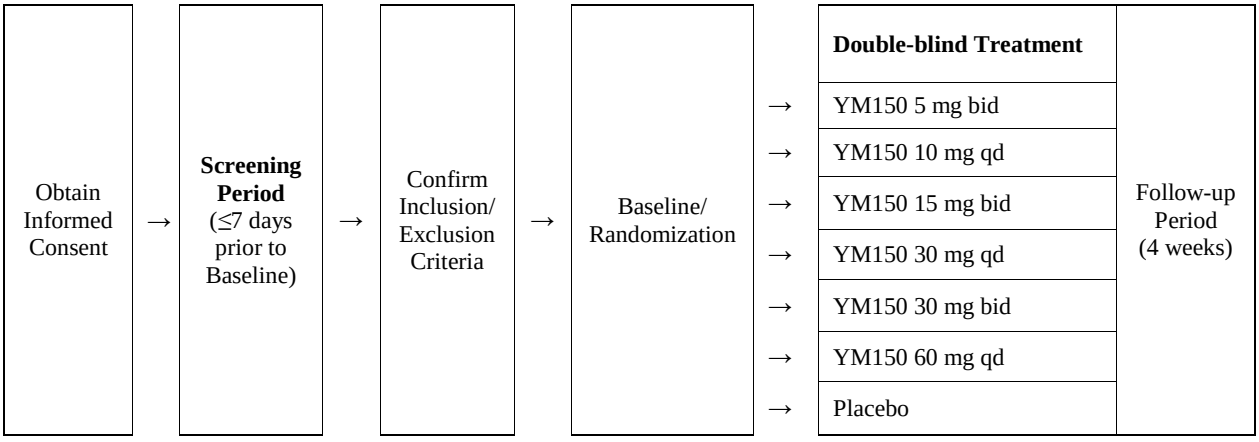
This Statistical Analysis Plan (SAP) contains a technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is finalized and signed prior to hard lock of the database.

# 2 FLOW CHART AND VISIT SCHEDULE

This study is a prospective, randomized, double-blind, multi-center, multiple dose, placebo controlled, parallel group study in patients presenting with an acute coronary syndrome (ACS). Patients will receive the study treatment at one of several possible doses, dependent on what they are randomized to, for 26 weeks in a double-blind treatment period, followed by a four week follow-up period.

A flow chart showing the study schematic and visits is presented below:

**Flow Chart**




**Start and End of Study**

The start of the study is defined as the time of the first patient's informed consent recorded on the informed consent form (ICF). The end of study is defined as the last patient's last protocol-defined assessment.

The schedule of assessments at each study visit is presented in Table 1: Schedule of Assessments below:

| | **Screening** [a] | **Baseline** [b] | **Double-blind Treatment Period** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **≤7 days prior to Randomization** | **Day 1** | **Day 3** | **Day 14** | **Week 6** | **Week 12** | **Week 18** | **Week 26 / Premature Discontinuation** | **4 Weeks after EOT** | **30 Weeks after Baseline** |
| **Visit Number** | **V1** | **V2** | **V3/TC** [c] | **V4** | **V5** | **V6** | **V7** | **V8/EOT/ VD** [d] | **FU** | **VD FU/TC** [e] |
| Allowance for visits (days) | -7 to 0 days Before V2 | 0 | 0/+2 | ±3 | ±4 | ±4 | ±4 | Within 4 days after last modification | | |
| Informed Consent/Authorization [f] | X | | | | | | | | | |
| Verify Inclusion/Exclusion Criteria | X | X | | | | | | | | |
| Medical History | X | X [g] | | | | | | | | |
| Height | | X | | | | | | | | |
| Weight | | X | | | | | | X | | |
| Vital Signs (SBP, DBP and pulse) | | X | X | X | X | X | X | X | X | |
| ECG | | X | X | X | X | X | X | X | X | |
| Pregnancy Test (females) | | X [h] | | | | X | | | X | |
| Physical Exam | | X | | X | X | X | X | X | X | |
| Chemistry/Hematology/Urinalysis [i] | | X | | X | X | X | X | X | X | |
| Local Laboratory | X [j] | X [k] | | | | | | | | |
| Pharmacodynamic Assessments [l] | | X | | X | X | | X | | X | |
| PK and PK/PD Sampling [m] | | | | X | X [n] | | X [o] | | | |
| Pharmacogenomic samples [p] | | X | | | | | | | | |
| Patient Reported Outcomes [q] | | X | | | | | | X | | |
| Randomization | | X | | | | | | | | |
| Study Drug Dispensing [r] | | X | | X | X | X | X | | | |
| Administration of Study Drug [s] | | X | X | X | X | X | X | X | | |
| Study Drug Accountability | | X | X | X | X | X | X | X | | |
| Previous & Concomitant Medications [t] | X | X | X | X | X | X | X | X | X | |
| Adverse Events [u] | | X | X | X | X | X | X | X | X | X [v] |
| Vital Status | | | | | | | | | | X |

**Table 1: Schedule of Assessments**

**Schedule of Assessments Footnotes**

a Screening information can be obtained from patient charts without an actual visit.

b Baseline procedures must be performed prior to first dose of study drug (patients should have first dose of YM150 study drug administered at the physician's office).

c Assessments only required for patients still in the hospital, except for Adverse Events (AE). AEs need to be collected at all times for which a telephone consult (TC) is allowed.

d Patient has to continue their double-blind treatment until patient comes for his/her End-of-Treatment (EOT) visit. In case a patient prematurely discontinues the study drug, the premature discontinuation visit (VD) should be performed within four days after discontinuation. Each patient will have a Follow-up (FU) visit 4 weeks after last dose of double-blind study drug.

e For patients who discontinue treatment prior to the week 26 V8 visit, a further follow-up visit, in addition to the follow-up visit 4 weeks after the VD visit, will be performed at the equivalent of week 30 from the baseline randomization visit to collect information on vital status of the patient. This can be performed by a telephone consult (TC) with the patient.

f Patient must have signed informed consent prior to any screening procedures being started.

g Any new signs and symptoms recorded since the informed consent form (ICF) was signed should be recorded as an AE.

h Pregnancy test (urine) must be negative within 72 hours prior to randomization. Pregnancy test will be analyzed at local laboratory or physician's office.

i To be analyzed at a central laboratory:
- Chemistry includes: sodium, potassium, calcium, chloride , inorganic phosphorus, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γGT), lactate dehydrogenase (LDH), total bilirubin, direct and indirect bilirubin, total protein, albumin and glucose. Total cholesterol and triglycerides will be measured at baseline only.
- Hematology includes: hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC), differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count
- Urinalysis includes: (microscopic) leucocytes, erythrocytes; (quantitatively) protein, glucose, creatinine.

j Serum creatinine at presentation of NSTE/STE-ACS, maximum troponin T/I and/or Creatine Kinase Myocardial Band (CK-MB) levels based on local laboratory results.

k ALT, estimated creatinine clearance (according to Cockcroft-Gault Equation) , total bilirubin for assessment of eligibility for randomization at baseline visit can be measured locally within max. 24h prior to randomization.

l PD samples will be analyzed at a central laboratory for: Prothrombin fragment 1+2 (F1+2), D-dimer, Factor Xa (FXa) Inhibition. At V2, V4 and FU one sample will be drawn for PD analysis only. At the other visits as described under points l, m and n below the PD sampling will be combined with PK sampling.

m Blood sample collection to analyze YM150 and its metabolite YM-222714. The first PK/PD sample is a random sample at V4 (Day 14) to be drawn during the regular visit. Separate PK/PD sampling will be performed in the morning at V5 and separate afternoon sampling will be performed at V7 (see points n and o below).This PK/PD sampling in the morning at V5 can be switched to V7 if more practical for the patient. In that case the afternoon sampling at V7 must be switched to V5. These two samples cannot be drawn during the same visit. If the PK/PD sample is not taken at V5 for any reason, then it can be taken as an unscheduled PK/PD sample at visit 6. This can be switched to an afternoon sample if more practical for the patient with the morning PK/PD sample then being taken at V7.

n Blood sampling for PK/PD assessment for V5 (Week 6) should be scheduled in the morning before 13:00: patient needs to be instructed not to take the morning dose at home. One PK and PD sample should be drawn before the morning dose is taken. The morning dose is taken at the investigational site before 13:00. The second PK and PD sample needs to be drawn 1-2 hours after the intake of the morning dose.

o Blood sampling for PK/PD assessment for V7 (Week 18) should be scheduled in the afternoon after 13:00: one PK and PD sample should be taken between 13:00 – 17:00 and the second sample to be taken 30 minutes later.

p One sample will be taken for analysis of coagulation related pharmacogenomic markers (2C19 polymorphisms) and for future analysis of potential relevant genes.

q EQ-5D and SF-36 data will be collected at V2 and EOT/VD, only in those countries where the translated questionnaires are available.

r Provide boxes of study drug to patients for self intake at home

s Patients need to take their study drug twice daily at home, except for the very first morning dose at the baseline day (V2) and the morning dose at the day of visit V5. At the baseline visit (V2) the first dose can also be taken in the evening if the patient is randomized in the afternoon. At V5 when PK/PD sampling needs to be performed in the morning (or at V7 if switched as discussed under point m above) the patient should not take the morning study drug at home but under supervision at the investigational site.

t Record all medications taken within 14 days of start of double-blind study drug, medications taken during the treatment period and through end of study.

u AEs will be collected from the time the ICF is signed through FU.

v At the VD FU/TC visit only AEs of death, MI, severe recurrent ischemia, stroke, systemic thromboembolic event and transient ischemic attack need to be collected.

Schedule of assessments during treatment period:

After the baseline visit the patients will have scheduled visits on Days 3 and 14 and Weeks 6, 12, 18, 26 (end of treatment [EOT]) and a follow-up (FU) visit 4 weeks after the EOT visit. At Day 3 a telephone consultation is allowed in case the patient has already been discharged from the hospital. If there is premature discontinuation of study drug for any reason, then the EOT visit will be performed, with the follow-up visit 4 weeks later. In addition, for premature discontinuation patients there will be an additional visit/telephone consultation at 30 weeks after baseline to collect information on the vital status of the patient and on AEs corresponding to efficacy endpoints (death, MI, severe recurrent ischemia, stroke, systemic thromboembolic event and transient ischemic attack). The scheduled visits can be performed with a window of 2-4 days (see Table 1 for further details).

Follow-up period:

After the end of double-blind treatment (Week 26) all patients will be followed for an additional 4 weeks and evaluated at the end of study visit, at week 30. During this FU period all patients will continue antiplatelet treatment as per (local) guidelines.

Additional follow-up for early withdrawals

The original study protocol (14 May 2009) followed subjects until 4 weeks after the end of treatment. This would be around week 30 for subjects completing the 26-week treatment period. For subjects that discontinued treatment early, the follow-up visit could be substantially earlier.

A protocol amendment (substantial amendment 01, version 2.0, 03 March 2010) was introduced to ensure that information on the vital status of the subject and on the efficacy related adverse events of death, myocardial infarction, severe recurrent ischemia, stroke, systemic thromboembolic event and transient ischemic attack are available for all subjects at the 30-week time point.

The recording of this additional information required the amendment to be approved, the subject to be contacted, and for the subject to consent. It is possible that lack of data (due to lack of consent, loss to follow-up) could be related to events or death – thus there could be some under-reporting in the additional follow-up period as it required retrospective consent. This data will not be included in the main (on treatment analysis), but may contribute to ITT analyses at later time-points (30 day data should be available for all subjects from the main study follow-up visit).

# 3 STUDY OBJECTIVE(S) AND DESIGN

## 3.1 Study Objective(s)

### 3.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of different doses and dose regimens of YM150 on top of standard treatment in the secondary prevention of Ischemic Vascular Events in patients with recent Acute Coronary Syndromes (ACS).

### 3.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of different doses and dose regimens of YM150 on top of standard treatment in the secondary prevention of Ischemic Vascular Events in patients with recent ACS,
- To compare safety, tolerability and efficacy of different doses and dose regimens of YM150 on top of standard treatment against Placebo,
- To assess PKPD properties in the target population,
- To further define the suitable patient population for further development (i.e. Phase III).

## 3.2 Study Design

This study is a prospective, randomized, double-blind, multi-center, multiple dose, placebo controlled, parallel group study in patients presenting with an ACS.

After patients have presented with the index event (ACS) they will be managed according to (local) standard of care which may include primary Percutaneous Coronary Intervention (PCI), thrombolysis and medical management. All patients will receive antiplatelet treatment per standard of care according to (local) guidelines (Bassand, 2007; Anderson, 2007):

- ASA 75-325 mg daily, as per local practice. It is recommended to use the lowest possible dose (i.e. 75-81 mg daily),
  or
- Clopidogrel 75 mg daily if ASA is contraindicated or not tolerated,
  or
- Combination of ASA 75-325 mg and clopidogrel 75 mg daily.

Patients will be screened for eligibility after presentation with the index event. If considered eligible, once stabilized, patients will be randomized in a double-blind fashion to one of seven study treatment groups within 7 days of presentation with the index event. The double-blind study drug will be given in addition to standard antiplatelet treatment as described above. Six dose groups of YM150 and one placebo control group will be evaluated in a double-blind fashion. Randomization will be stratified by country and clopidogrel use. Patients will receive double-blind treatment with YM150 or placebo for a total duration of 26 weeks.

The allocation ratio will be 1:1:1:1:1:1:2 to one of the following groups:

- Group 1: YM150 5 mg bid,
- Group 2: YM150 10 mg qd,
- Group 3: YM150 15 mg bid,
- Group 4: YM150 30 mg qd,
- Group 5: YM150 30 mg bid,
- Group 6: YM150 60 mg qd,
- Placebo.

Patients should be randomized as early as possible after clinical stabilization, but after discontinuation of parenteral antithrombotics (see section 5.1.3 for specific details). In any case, patients need to be randomized within 7 days after presentation of the index event. The first dose of double-blind study drug will be given in the morning or afternoon of the baseline visit.

## 3.3 Randomization

Patients, who meet the inclusion/exclusion criteria, will be randomly assigned to receive either daily oral YM150 (5 mg bid, 10 mg qd, 15 mg bid, 30 mg qd, 30 mg bid or 60 mg qd), or placebo using 1:1:1:1:1:1:2 randomization schedule.

Randomization will be stratified by country and by the type of standard antiplatelet treatment at baseline (either Clopidogrel or No Clopidogrel).

Assignment to treatment groups will be done using the randomization scheme prepared by IFE Europe GmbH, Germany, under the responsibility of the Clinical Data Sciences Department of Astellas.

To obtain a patient number and the randomized treatment as appropriate, the pharmacist or designee will utilize a randomization system available seven days a week and 24 hours a day (phone or web-based). After submitting certain information about the eligible patients, the assigned medication identified by kit number and patient number will be provided. Study drug assignment will remain blinded to all staff. If a patient is assigned a study drug and a patient number, but does not receive study drug, the patient number will not be used again.

# 4 SAMPLE SIZE

One hundred and fifty eight (158) patients will be randomized to each YM150 dose group and 316 patients to the placebo group, for a total of 1264 patients randomized.

Assuming the incidence of Major and CRNM bleeding events [International Society of Thrombosis and Hemostasis (ISTH) definition] at six months will be 3% for placebo and 4%, 7% and 9% for YM150 10, 30 and 60 mg per day respectively, this sample size will allow a 91% test power to detect a linear trend in the mentioned incidence versus daily dose, using a two-sided test with 95% confidence level.

Previous studies suggest that approximately 5% of patients are expected to withdraw due to other reasons (censored for the primary endpoint) during the first days of double-blind

treatment and will provide almost no information for the primary analysis. In addition, another 10% of patients are expected to be censored after the first month, so they will contribute, on average, information for around half of the six months study period. This has been taken into account as well for the sample size calculation given above.

# 5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9 (5), the following analysis sets will be used for the analyses.

## 5.1 Full Analysis Set (FAS)

The Full Analysis Set consists of all randomized patients who received at least one dose of randomized study drug.

The selection of patients for the FAS will be confirmed in the Blind Data Review Meeting (BDRM).

The FAS will be used for summaries and primary analyses of efficacy data, as well as selected demographic and baseline characteristics.

## 5.2 Per-Protocol Set (PPS)

The Per-Protocol Set includes all patients of the FAS who have no major protocol violations listed in Section 5.2.1 of this SAP.

Final judgments on exclusion of patients from the PPS, based on protocol violations, are to be made at the BDRM, held prior to unblinding.

The PPS will be used for secondary analyses of selected efficacy endpoints and the primary safety endpoint.

### 5.2.1 Major Protocol Violations

The following protocol violations might lead to exclusion from the PPS. The violations and potential violations will be reviewed at the BDRM, and the final decisions documented in the BDRM minutes prior to database lock and unblinding.

1. Any dosing error for study medication (incorrect medication kit) or suspected dosing error
2. Tablet treatment compliance of YM150/YM150 PTM tablets over the double-blind period of less than 80 % or > 125%
3. Any other surgical or non surgical procedure which may affect the assessment of the anticoagulant effect of the study drug
4. Administration of forbidden concomitant medications as defined in Appendix 1 for more than 7 days between first and last dose of study medication inclusive: Anticoagulant agents, thrombolytics or other antiplatelet agents - excluding ASA, ASA derivatives, Clopidogrel or NSAIDS.
5. Violation of inclusion 1, 2, 3, 4, 6 or 7 or exclusion criteria 1, 3, 5, 7, 11, 12 or 13.

- For inclusion criteria 2 ["Has elevated biomarkers (cardiac Troponin T or I or CKMB) >2xULN for CK-MB or >ULN for troponin"] – subjects will be excluded from the PPS if there is no positive biomarkers and no PCI for the index event.

6. Patients not withdrawn from treatment and/or study despite having met specified criteria for withdrawal.
7. Any evidence of unblinding, including measurement of coagulation during double blind treatment.

Prohibited and restricted medications will be reviewed on a case by case basis in the BDRM, and will include details on the dose administered, the length of time the patient received treatment and the indication. The final decision on whether the prohibited medication constitutes a major protocol violation will be confirmed at the BDRM. Further details of prohibited medications can be found in Section 7.2.4, Appendix 1 of the study protocol and Appendix 1: List of Excluded and Restricted Previous and Concomitant Medication of this SAP.

Violation of washout times (see Appendix 1 of this SAP) will not be considered a Major Protocol Violation. Use of antithrombotic agents apart from ASA/clopidogrel after the first dose of study drug will be considered on a case-by case basis. In general, cumulative use of antithrombotics for > 7 days between 1st and last dose of study drug will be considered a major protocol violation. Days on which study drug was interrupted will not be counted.

## 5.3 Safety Analysis Set (SAF)

The Safety Analysis Set consists of all randomized patients who received at least one dose of randomized study drug.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

## 5.4 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetics Analysis Set includes patients who received at least one dose of the active treatment for whom at least one sample was collected for measurement of drug concentration and for whom the time of sampling and the time of dosing on the day of sampling is known.

Some patients may be excluded from this analysis set if it is found that confounding factors affect the pharmacokinetic results (including protocol violations and deviations).

At the discretion of the pharmacokineticist a serum YM150 concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason. In either case, specific reasons for data being excluded from the analysis will be provided in a separate document and the potential impact on the interpretation of study outcome will be discussed in the PK report.

The PKAS will be used for all tables and graphical summaries of the PK and PD data.

Full details for exclusions from the PKAS will be specified in the pharmacokinetic analysis plan.

## 5.5 Analysis of Subgroups

**Age Subgroup**

Subgroup analyses will be performed on an 'Age' subgroup. The subgroup will be defined based on the patients age at Screening (Visit 1) which will be taken directly from the eCRF 'Demography' page and will fall into three mutually exclusive categories:

- <65 years of age,
- Greater than or equal to 65 and <75 years of age.
- Greater than or equal to 75 years of age.

The age subgroups will be used to summarize the overall incidence of bleeding events.

**Gender Subgroup**

Subgroup analyses will be performed based on the patients' gender. The gender subgroups will be used to summarize the overall incidence of bleeding events.

# 6 ANALYSIS VARIABLES

## 6.1 Efficacy and Composite Variables

### 6.1.1 Adjudicated Efficacy Events

The presence/absence of the following events combined with the time of the first occurrence or time of censoring will be considered to be the efficacy variables for this study; note that only the occurrence of the first event in a subject of a particular type will be of interest as typically the subject may leave the study or the hazard function may change after the first event:

- Systemic thromboembolic events (STEs),
- Deaths,
- Myocardial infarction (MI),
- Severe recurrent ischemia,
- Stent Thrombosis,
- Stroke,
- Transient Ischemic Attacks (TIA),

For example, when considering MIs, only the first MI in the period will be of interest – the subject will be excluded / censored after that. A previous bleeding event will not affect the analysis of MIs.

Each of the above events will be adjudicated and classified by the Independent Adjudication Committee (IAC). For each of the above events, the adjudication committee will review the data provided by the investigators and determine which event (if any) the patient experienced. The adjudication committee will remain blinded throughout the treatment period and will

objectively review the data available. Definitions for each of these events are given in the study protocol and further detailed in the IAC charter.

For each of the above events the adjudication committee will provide further classification of the exact nature of the event, and may also provide a sub-categorization.

Myocardial infarction (MI) will be adjudicated and categorized as:

- STEMI (ST segment elevation MI)
- NSTEMI (Non ST segment elevation MI)
- Diagnostic ECG unavailable

Myocardial infarction (MI) will also be adjudicated and categorized as:

- Fatal MI
- Non-fatal MI

Myocardial infarction (MI) will also be adjudicated and categorized as:

- Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection.
- Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension or hypotension.
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new Left Bundle Branch Block (LBBB), or evidence of fresh thrombus in a coronary artery by angiography and / or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4a: Myocardial infarction associated with PCI.
- Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.
- Type 5: Myocardial infarction associated with Coronary Artery Bypass Graft (CABG).
- Type 1 or 2
- Type 1, 2 or 4b
- Silent MI (These are not sub-classified into types 1 to 5. Silent MIs should be presented separately, and not to be counted with other MIs).

Note: for the individual criteria for the adjudication of MI Type 1, 2 and 4b, sometimes there is insufficient information to determine which category, so an event might be classified as "Type 1, 2 or 4b" for example. The adjudication process involves handling cases known as myocardial re-infarction, in which an MI occurs shortly after a preceding MI from which biomarkers are still elevated. This situation requires the use of particular adjudication criteria, but the adjudication conclusion is the same as any other MI and is classifiable as types 1, 2 or 4b. To all intents and purposes, the fact that it is a myocardial re-infarction can be

disregarded – the only features to present are fatal/non-fatal, STEMI/non-STEMI and types 1 to 5 as with any other MI. For the purposes of analyses, re-infarctions will be treated like any other adjudicated MI (except silent MIs) – and in general the preceding MI will be the event that counts as it will be the first event.

Systemic thromboembolic and severe recurrent ischemia will be confirmed by the IAC and no further classifications will be provided.

Patients without a stent will be adjudicated as "not applicable" for the Stent Thrombosis variable. For those subjects with a known stent or where the presence of a stent is unknown, Stent Thrombosis will be adjudicated and further categorized as:

- Definite Stent Thrombosis,
- Probable Stent Thrombosis,
- Possible Stent Thrombosis.

Deaths will be categorized as:

- Cardiovascular death,
- Non-Cardiovascular death,
- Death of unknown cause. These will be presumed cardiovascular.
- Cardiovascular deaths and deaths of unknown cause will be presented

Cardiovascular Deaths will be further categorized as:

- Sudden cardiac death,
- Death due to acute MI,
- Death due to heart failure or cardiogenic shock,
- Death due to cerebrovascular event (intracranial hemorrhage or non-hemorrhagic stroke),
- Death due to other cardiovascular causes.

Each stroke event occurring in the study will be categorized (or sub-categorized) by the IAC as:

- Ischemic stroke:
  - cardioembolic stroke (includes definite and probable),
  - noncardioembolic stroke (includes possible lacunar stroke, possible atherothrombotic stroke and miscellaneous specific causes),
  - Ischemic – uncertain.
- Stroke of unknown etiology:
  - Hemorrhage excluded,
  - Hemorrhage not excluded.
- Hemorrhagic strokes (Safety variable)

Stroke will be also categorized as:

- Disabling stroke (which includes all fatal strokes)
- Non-disabling stroke

and also as:

- Fatal stroke
- Non-fatal stroke

TIAs will be confirmed by the IAC and no further classifications will be provided.

Each of the above categories and sub-categories will be provided directly by the IAC and will form the efficacy endpoints of the study together with the composite endpoints defined in Section 6.1.2.

### 6.1.2 Combination of Adjudicated Events (composites)

The presence/absence of composite events combined with the time of the first occurrence or time of censoring will be also considered for the following:

**All cause mortality**

Including all deaths, cardiovascular, non-cardiovascular and deaths of unknown cause.

**Stroke, MI, Severe Recurrent Ischemia and Death**

The composite incidence of any non-fatal MI, non-fatal stroke, severe recurrent ischemia, and all deaths will be defined based on the decisions provided by the IAC at 30 days and 6 months.

**Stroke, MI and Death**

The composite incidence of any non-fatal MI, non-fatal stroke, and all deaths will be defined based on the decisions provided by the IAC at 30 days and 6 months.

**Stroke, MI, Ruby-1 Modified ISTH Major Bleeding Events and Death**

The composite incidence of any non-fatal MI, non-fatal stroke, Ruby-1 Modified ISTH major bleeding events (see list of key terms and section 6.2.1), and all deaths will be defined based on the decisions provided by the IAC at 30 days and 6 months.

**Hospitalization**

Hospitalization will be defined to be any event which occurs and leads to the hospitalization of the patient. Hospitalization will be recorded on the hospitalization records page of the eCRF. Details of the date of admission, date of discharge (or if ongoing), reason for hospitalization, and further details if it is a routine visit will be captured.

For each hospitalization stay, the duration will be calculated to be:

Date of discharge – Date of Admission + 1

In addition, the total days of hospitalization during the double-blind treatment will be calculated as the sum of all durations of hospitalization for that patient up to the end of the treatment period (up to and including the day after the last dose). Subjects with no hospitalization during the double-blind period will have a total duration of hospitalization of zero.

If the patient was admitted and discharged on the same day the stay will be 1 day.

For any partial dates the worst case scenario will be applied, that is the first day of the month will be assumed for admission and the last day of the month for discharge.

### 6.1.3 Time to Event Calculations

Start of periods

Periods will start at the date and time of the first dose. If the time is unknown, periods will start on the day of first dose (in which case they will include all events on first dose except those marked in the CRF as starting before the first dose).

Note that deaths will be analyzed using the onset date according to the following rules:

1. Use the adjudicated date for the death if this is during (or before) the treatment period
2. If the adjudicated date for the death is after the treatment period, use the (earliest) adjudicated onset date for an adjudicated fatal event (excluding any events starting before the first dose)
3. For deaths without a corresponding adjudicated event in (2), the adjudicated date of death will be used.

Date of last dose

If the date of last dose is missing, then the date of end of treatment visit will be used – or the date of last visit if there is no end of treatment visit.

If the date of last dose is partial, then the last date consistent with the information provided (e.g. last day of month or last day of year) will be used, unless this is after the date in the previous paragraph.

Note that the last dose, the treatment period and compliance are calculated including periods of dose interruption in the treatment period. Dose interruptions will be listed.

Time to Event Calculations (main analysis)

For all analyses detailed in Sections 7.4.2, 7.5.1 and 7.5.2 (time to event analyses), the time to event of the event of interest will be calculated (in days) as:

(1 + First event date– Date of first dose).

where date of first dose is defined as stated in Section 6.7

For patients who have experienced more than one event of a particular type, only their first event following study treatment will be used in the analysis.

If an event occurs after the last dose of double blind treatment then the event will be regarded as on treatment (i.e. not censored) only if it occurs on the day after the last dose of double blind treatment. Otherwise it will be regarded censored on the day after the last dose.

Patients who have not experienced an event during the double-blind treatment period will be censored; the patient will be censored on the day after the last dose of double blind treatment. Time to censoring will be calculated in days as:

(2 + Date of last DB dose - Date of first DB dose)

- For analyses at 30 days, patients who have not experienced an event on or before Day 30 will be censored at Day 30 (or final follow-up visit if that is earlier).
- For analyses at six months including amendment 1, patients who have not experienced an event on or before Day 182 will be censored at Day 182 or at their final follow-up visit if that is earlier.

Time to Event Calculations for the intent-to-treat (ITT) analysis

An additional sensitivity analysis will also be conducted, where the patient will be defined to have had an event, if the event occurs at any time after the first dose (either during the double-blind treatment period or the follow-up period). Similar definitions to above will be used where the last available contact date (e.g. follow-up visit) is used instead of the day after the last dose (i.e. censored time to event calculated as

1 + last of(date of last visit, last evaluation, last event) – date of first dose.

ITT summaries and analyses may include events up to Day 30, Week 26 (Day 182), week 30 (Day 210), or in the follow-up period (up to 7 or 30 days after the end of the treatment period).

Time to Event Calculations for the PPS analysis

Similar definitions to above will be used for the efficacy analysis based on the PPS. However, patients who have an event after their major protocol violation, will be counted as not having had an event and will be censored at the time of their major protocol violation (i.e. censored time to event calculated as

1 + onset date of the first major protocol violation – date of first dose).

The PPS analyses will only include time to the last dose of double-blind study treatment.

## 6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Bleeding events
- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug)
- Clinical laboratory variables (hematology, biochemistry, and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- Physical examination
- 12-lead electrocardiogram (ECG).

### 6.2.1 Primary Safety Variable

The primary safety variable will be the presence/absence of the composite of bleeding events at six months (combined with the time of first occurrence or time of censoring) of:

- Major bleeding events
- Clinically relevant non-major .(CRNM) bleeding events

during the double-blind treatment phase according to the Ruby-1 modified ISTH criteria defined in the study protocol. [This is the definition in the protocol – when setting up the adjudication process; it became apparent that the definition was not quite the same as the ISTH criteria. The definition in the protocol has been labeled "Ruby-1 modified ISTH criteria" and used as primary. The unmodified ISTH criteria are used as a secondary variable]. These events will be determined by the IAC. The primary endpoint will be the first occurrence of either of the events specified above.

All overt bleeding events will be reported by the investigator and adjudicated according to the Ruby-1 modified ISTH definitions and classified by the IAC to:

- Major bleeding,
- CRNM bleeding,
- Minor bleeding.

Details on the adjudication process are described in the IAC Charter. The classifications of bleeding events are detailed in Section 2.3.1 of the protocol. All bleeding events will be reported via AE reporting and through specific questions at each visit and will be sent to the IAC.

For the primary endpoint, the Time to Event variable will be calculated following the same rules as defined in Section 6.1.3.

Analogous definitions to Section 6.1.3 will also be used for time to event calculations for the PPS (the percentage of data included in the PPS analysis is further discussed in Section 5.2).

The blood transfusion log on the eCRF will capture information on details of any transfusions required, start/stop date/time, the source, blood product required, the number of units and the reason for transfusion. This information will be used by the IAC to help in determining bleeding events.

### 6.2.2 Secondary Safety Variables

The secondary safety variables will be the first occurrence of each of the following variables as classified by the Ruby-1 modified ISTH criteria:

- Composite of major and CRNM bleeding events at 30 days,
- Major bleeding events at 30 days and 6 months,
- CRNM bleeding events at 30 days and 6 months,
- Minor bleeding events at 30 days and 6 months,
- All bleeding events at 30 days and 6 months.

The events will be adjudicated and determined by the IAC. Time to event for each of the above events will be calculated as per the primary safety endpoint.

Bleeding events will also be classified separately, by the Independent Adjudication Committee (IAC), according to the following definitions:

a) Original International Society on Thrombosis and Haemostasis (ISTH) definitions (6).
b) Thrombolysis in Myocardial Infarction (TIMI) classification (1). .

For the ISTH definitions, the categories are the same ones as per the Ruby-1 modified ISTH, whereas for the TIMI classification the bleeding events will be classified and reported using the following categories:

- Composite of TIMI major and TIMI minor bleeding events at 30 days and 6 months,
- TIMI major bleeding events at 30 days and 6 months,
- TIMI minor bleeding events at 30 days and 6 months
- TIMI bleeding events requiring medical attention at 30 days and 6 months
- TIMI insignificant bleeding events at 30 days and 6 months,
- All bleeding events (excluding the ones classified as TIMI insignificant bleeding events) at 30 days and 6 months.

Other Intracranial hemorrhages will be categorised as:

- Subarachnoid Hemorrhage
- Subdural Hematoma
- Epidural Hematoma

### 6.2.3 Adverse Events

Frequency, nature and severity of AEs - Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).

Any adverse events will be recorded on the eCRF. Details of the event, including start and stop date/time, outcome, severity, whether the event was serious or not (including reason considered serious), action taken, whether additional treatment was required and relationship to study drug will be recorded.

A treatment emergent adverse event will be defined as any adverse event which starts or increases in severity after the first administration of the test drug/comparator drug. If an adverse event occurs after the last dose of double blind treatment then the event will be regarded treatment emergent.

If the adverse event onset date is either missing, partial or with an unknown time, then the adverse event analysis onset date/time will be used. The adverse event analysis onset date/time will be calculated as detailed in Table 2.

**Table 2 Definition of the *Analysis Adverse Event Onset Date* and *Analysis Adverse Event Onset Time* (AESADTM)**

| Variables from the CRF | | | Derived variables | |
|---|---|---|---|---|
| AE onset date | AE onset time | CRF start reference variable [AESTRF] | Analysis AE onset date | Analysis AE onset time |
| Complete | Complete | Not used | AE onset date | AE onset time |
| Complete and before first DB treatment intake date | unknown | Not used | AE onset date | 23:59 |
| Complete and after first DB treatment intake date | unknown | Not used | AE onset date | 00:00 |
| Complete and on the same day as first DB treatment intake date | unknown | "before first dose of study drug" | AE onset date | 00:00 |
| Complete and on the same day as first DB treatment intake date | unknown | "after first dose of study drug" or missing AESTRF | AE onset date | Analysis Time of the first DB treatment intake date (time in ADSL.EXSTADTM) |
| Partial and before first DB treatment intake date (e.g. AE onset is UN/Sep/2009 and first DB treatment intake is 12/Oct/2009) | unknown | Not used | Last day compatible with the partial date (e.g. UN/Sep/2009 imputed as 31/Sep/2009) | 23:59 |
| Partial and after first DB treatment intake date (e.g. AE onset is UN/Sep/2009 and first DB treatment intake is 12/Aug/2009) | unknown | Not used | First day compatible with the partial date (e.g. UN/Sep/2009 imputed as 1/Sep/2009) | 00:00 |
| Partial and compatible with first DB treatment intake date (e.g. AE onset is UN/Sep/2009 and first DB treatment intake is 18/Sept/2009) | unknown | "before first dose of study drug" | Analysis Date of the first DB treatment intake date (date in ADSL.EXSTADT) | 00:00 [This will ensure that the imputed time is before the DB treatment time] |
| Partial and compatible with first DB treatment intake date (e.g. AE onset is UN/Sep/2009 and first DB treatment intake is 18/Sept/2009) | unknown | Missing or "after first dose of study drug" | Analysis Date of the first DB treatment intake date (date in ADSL.EXSTADT) | Analysis Time of the first DB treatment intake date (time in ADSL.EXSTADTM) |
| Missing | unknown | "before first dose of study drug" | Analysis Date of the first DB treatment intake date (date in ADSL.EXSTADT) | 00:00 [This will ensure that the imputed time is before the DB treatment time] |
| Missing | unknown | Missing or "after first dose of study drug" | Analysis Date of the first DB treatment intake date (date in ADSL.EXSTADT) | Analysis Time of the first DB treatment intake date (time in ADSL.EXSTADTM) |

If a patient experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date).

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1.

Any bleeding events, suspected or confirmed strokes, suspected or confirmed TIAs, suspected or confirmed STEs, suspected or confirmed MIs, suspected or confirmed severe recurrent ischemia will be recorded on the eCRF under the relevant adverse event section. Any AEs captured on these pages will be documented as adverse events and summarized accordingly.

### 6.2.4 Vital Signs

The following endpoints will be assessed:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Pulse rate
- Change from baseline in SBP, DBP and pulse rate

The position and date of the assessment will also be recorded. Change from baseline will be calculated to be the measurement taken at the study specific visit minus the baseline visit. For definitions of Baseline please see Section 7.9.3

Weight will also be recorded at Baseline and Week 26.

### 6.2.5 ECG

ECG recordings including date and time of assessment and the investigator interpretation of the reading (normal, abnormal not clinically significant, abnormal clinically significant) will be recorded. In addition the assessment of abnormality and type of abnormality from the central reading will also be recorded.

Any ECG recordings which are considered to be abnormal and clinically significant will be further detailed as an adverse event unless it is considered related to the baseline condition. In addition to the scheduled central ECG assessments, local measurements may be conducted at unscheduled visits if considered necessary by the investigator.

The following variables will be recorded by the central laboratory; PR, QRS, QTcB, QTcF, QT, RR (ms) and Heart Rate. The change from baseline for each visit will be calculated, along with the minimum and maximum post-baseline values occurring per patient in the double-blind treatment period.

### 6.2.6 Physical Examination

A physical examination will be performed on the patient at Baseline, and will document any abnormalities on each of the body systems; General Appearance, Skin (incl. hair and nails), Ears, Nose, Throat, Eyes, Neck (incl. Thyroid), Cardiovascular (incl. peripheral vascular pulsations), Chest/Lungs, Abdomen, Musculoskeletal, Neurological Status (incl. reflexes), Breast (optional), Genitourinary (optional), Rectal (optional), Other Relevant Examinations. Any changes in physical examination will be recorded at subsequent visits, with details of any clinically significant changes.

### 6.2.7 Laboratory assessments:

- Laboratory assessments (hematological, biochemical, urinalysis, hepatic, renal and cardiac parameters).
- Change from baseline for each of the numeric laboratory assessments. For definitions of Baseline please see Section 7.9.3.

If the patient has more than one sample for the visit, the mean value will be used.

The normal ranges used in the presentation of the laboratory results will be based on the age at screening.

The creatinine clearance will be calculated using the Cockcroft-Gault equation. The calculation will use the weight from the eCRF (RAVE).

<u>For creatinine measurements in mg/dl:</u>

For Men:

$$\text{Creatinine Clearance} = \frac{(140\text{-Age}) \times \text{Weight in kg}}{72 \times \text{Serum Creatinine}}$$

For Women:

$$\text{Creatinine Clearance} = \frac{(140\text{-Age}) \times \text{Weight in kg}}{72 \times \text{Serum Creatinine}} \times 0.85$$

Source: Cockcroft and Gault, 1976

<u>For creatinine measurements in µmol/l:</u>

For men:

$$\text{Creatinine Clearance} = \frac{(140\text{-Age}) \times \text{Weight in Kg} \times 1.23}{\text{Serum Creatinine}}$$

For women:

$$\text{Creatinine Clearance} = \frac{(140\text{-Age}) \times \text{Weight in Kg} \times 1.04}{\text{Serum Creatinine}}$$

For Creatinine Clearance, the worst post-baseline value will be defined to be the lowest recorded value.

Hemoglobin laboratory parameters may also be assessed by local laboratories if considered necessary by the investigator at unscheduled visits. The result will be recorded along with whether it was within normal limits.

A urine pregnancy test will be taken at Baseline, Week 12 and Follow-up, patients continuing in the study should have a negative result, or be of non-childbearing potential. Pregnancy tests may also be conducted at unscheduled time points at the discretion of the investigator.

The decrease in hemoglobin will be calculated for any bleeding AEs confirmed by the IAC. The start date/time of the AE will be used to identify the last hemoglobin assessment taken in the study prior to commencement of the bleeding event. The stop date/time of the bleeding event will be used to identify any hemoglobin measurements taken within 24 hours after the cessation of bleeding. For the calculation, the minimum hemoglobin value within this time window will be used. If the hemoglobin measurement is outside this window, the first measurement following cessation of bleeding will be used.

The number of units transfused over the time period will be defined to be the sum of any units transfused from the date of the last hemoglobin assessment taken in the study prior to commencement of the bleeding event to the date of the measurement used above as the post bleeding hemoglobin value. The number of units will be taken directly from the Blood Transfusion Log of the eCRF and will include any blood products which are transfused. Hemoglobin values will be converted to the same units as the units used on the blood transfusion log.

The observed decrease in hemoglobin concentration (units) will be calculated as:

Hemoglobin value prior to bleeding AE – Hemoglobin value after bleeding event

The total estimated decrease in hemoglobin concentration (units) will be calculated as:

Observed decrease in hemoglobin + number of units transfused in the time period

Hemoglobin concentration is used in g/dL. In this calculation a drop of 1 g/dL is equivalent to 1 unit of blood.

### 6.2.8 Mortality Reports

A mortality report will be completed for any deaths which occur in the study, this will serve as an aide to the IAC and will not be used for any of the analyses. The date and time of death will be recorded, along with the cause and relationship of the study drug to the death.

### 6.2.9 Rankin Scale

The Modified Rankin Scale should be completed at 30 days or at hospital discharge (following hospitalization for stroke), whichever comes first. The Modified Rankin Scale will record the overall score and date of assessment.

### 6.2.10 Diagnostic Imaging

Diagnostic Imaging may be conducted at unscheduled visits, if considered necessary by the investigator. The date and time the examination was performed, the type of imaging, why it was conducted i.e. in relation to which AE, the result and any comments.

### 6.2.11 Hepatic Monitoring

Hepatic monitoring visits must be conducted when moderate or marked abnormalities are observed on the central laboratory results and might also be conducted at the discretion of the investigator. Signs and symptoms of any hepatic events will be recorded and include; abdominal pain, fever, chills, nausea, vomiting, rash, hepatic enlargement on palpation, pain in epigastrio, tenderness of the liver, if any of the above events are observed they will be further recorded as an AE.

Blood samples may also be taken for monitoring of viral hepatic markers, further diagnostic imaging conducted, concomitant medications recorded, in particular paracetamol use which may be relevant to liver function abnormalities, or any other medications or changes in medication which could be relevant. Herbal remedies will also be recorded, along with alcohol use, any auto-immune diseases, underlying metabolic and genetic disorders which may have caused hepatic abnormalities.

Further information collected will be any hemodynamic events (which will also be recorded as an AE), laboratory tests including liver function tests and the patient's hepatic status including the investigator's opinion on a possible cause.

### 6.2.12 Renal Monitoring

Renal monitoring visits will be conducted when there is a moderate or marked renal abnormality. Signs and symptoms of any renal events will be recorded, along with renal status, and if necessary laboratory testing (including serum creatinine) and diagnostic imaging.

## 6.3 Pharmacokinetic Variables

Blood samples will be collected for determination of YM150 and YM-222714 plasma concentrations. Sampling times defined in Note m of Table 1: Schedule of Assessments.

Information regarding the pharmacokinetic analysis will be described in a separate PK and PD analysis plan.

## 6.4 Pharmacodynamic Variables

For the purpose of analyzing biomarkers (F1+2, D-dimer and FXa inhibition) blood samples (2.7 mL citrate tubes each) will be obtained from all patients. Blood samples for assessment of F1+2, D-dimer and FXa inhibition will be collected at seven time points during five visits in total. Sampling times defined in Note n of Table 1: Schedule of Assessments.

Information regarding the pharmacodynamic analysis will be described in a separate PK and PD analysis plan.

## 6.5 Pharmacogenomic Variables

One blood sample at V2 will be taken at baseline to specifically analyze 2C19 polymorphisms.

Information regarding the pharmacogenomic analysis will be described in a separate PK and PD analysis plan.

## 6.6 Patient Reported Outcomes

Patients will complete the following questionnaires:

- EuroQol – 5 Dimension Questionnaire (EQ-5D)
- The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

These are described in more detail in the sub-sections below. EQ-5D and SF-36 data will be collected at Baseline and EOT/VD only in those countries where the translated questionnaires are available.

### 6.6.1 EQ-5D

Secondary efficacy variables from EQ-5D are the change from Baseline to Endpoint in:

- EQ-5D Mobility Score
- EQ-5D Self-Care Score
- EQ-5D Usual Activities Score
- EQ-5D Pain/Discomfort Score
- EQ-5D Anxiety/Depression Score
- EuroQol – Visual Analog Scale (EQ-VAS) Score

The EQ-5D is an international standardized non-disease specific (i.e. generic) instrument for describing and valuing health status. It is a multi-dimensional measure of health-related QoL, capable of being expressed as a single index value (the utility score) and specifically designed to complement other health status measures. The EQ-5D has 5 domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each domain is a single item of 3 response levels assigned to a 1 to 3 value (see Table 3).

**Table 3 Response level values for the EQ-5D questionnaire**

| EQ-5D Domain | | Response level value | | |
|---|---|---|---|---|
| **no** | **Label** | **1 'No Problems'** | **2 'Some Problems'** | **3 'Unable to perform the activity'** |
| 1 | Mobility | I have no problems in walking about | I have some problems in walking about | I am confined to bed |
| 2 | Self care | I have no problems with self-care | I have some problems washing or dressing myself | I am unable to wash or dress myself |
| 3 | Usual activities | I have no problems with performing my usual activities | I have some problems with performing my usual activities | I am unable to perform my usual activities |
| 4 | Pain/discomfort | I have no pain or discomfort | I have moderate pain or discomfort | I have extreme pain or discomfort |
| 5 | Anxiety/depression | I am not anxious or depressed | I am moderately anxious or depressed | I am extremely anxious or depressed |

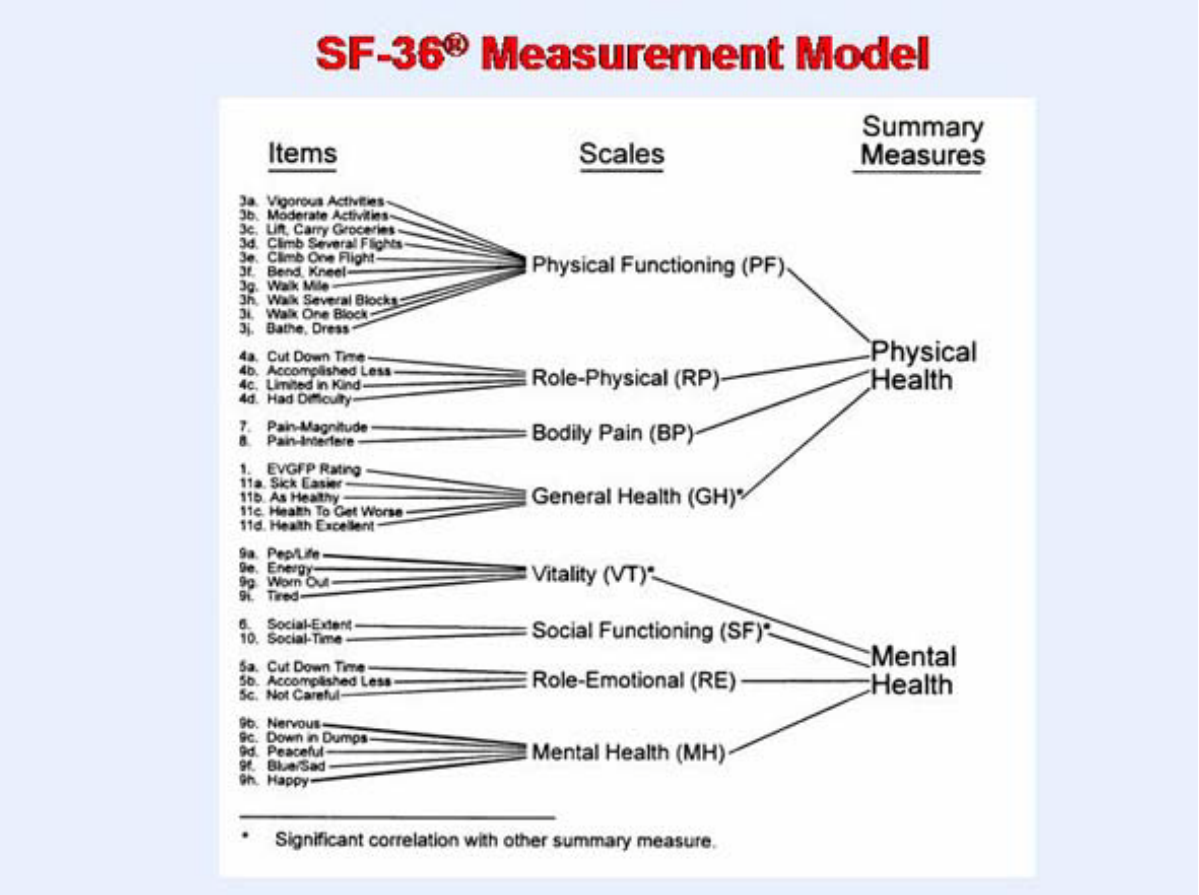
In addition, the EQ-5D has a visual analogue scale (EQ-VAS) that elicits a self-rating by the respondent of his health status. The EQ-VAS is recorded by the patient of his health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' (=100) and 'Worst imaginable health state' (=0).

### 6.6.2 SF-36

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

The SF-36 contains 36 items that measure eight dimensions:

1. physical functioning (PF);
2. role limitations due to physical health problems (RP);
3. bodily pain (BP);
4. social functioning (SF);
5. general health perceptions (GH);
6. role limitations due to emotional problems (RE);
7. vitality, energy or fatigue (VT); and
8. mental health (MH).




Among the 36 items, the items that measure physical functioning, role functioning (physical), bodily pain, and general health perceptions comprise the physical health composite summary (PCS); whereas items that measure vitality, social functioning, role functioning (emotional), and general mental health comprise the mental health composite summary (MCS).

**Table 4 Transformation of SF-36 items to a scale from 0 to 100**

| Question | Self-perceived health | |
|---|---|---|
| | 0 (Poor) | 100 (Better) |
| 1, 2, 6, 8, 9a, 9d, 9e, 9h, 11b, 11d | 5 | 1 |
| 3a to 3j | 1 | 3 |
| 4a to 4d, 5a to 5c, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c | 1 | 5 |
| 7 | 6 | 1 |
| Programming note: Once transformed – the items should each span the range 0 to 100, and should be positively correlated with each other. | | |

Item scores for each dimension are coded, summed and transformed to a scale from 0 to 100, with higher scores indicating better self-perceived health (See detail in Table 4). The transformed items are then averaged to give the subscales. The subscales are averaged to give the composite scores. The composite scores are averaged to give the overall score. The

reliability and validity of the SF-36 is well documented in a variety of different patient groups, including patients with vascular diseases.

For each of the 8 dimensions, if less than 50% of the items which constitute that dimension are missing, the dimension score will be calculated by the mean of the available non-missing items. The physical health composite summary (PCS) and mental health composite summary (MCS) will only be calculated if a score has been calculated for all 4 dimensions that constitute the composite summary. The overall score will only be calculated if both physical and mental health composite scores are available – i.e. if scores are calculated for all 8 dimensions.

### 6.6.3 Health Care Resource Use, Cost-effectiveness and Utility / QALY scores

The following endpoints associated with resources and cost effectiveness will be calculated:

- The health care resource use associated with both treatment options; and
- The cost-effectiveness associated with both treatment options.

The health care resource use, as well as the cost-effectiveness of the treatment options will be addressed in so called Cost-Effectiveness and/or in Cost-Utility Models. The Cost-Utility models will provide estimates on Cost per QALY. These types of models and Cost per QALY estimates are used by HTA (Health Technology Assessment) bodies, such as UK NICE.

The utility score is derived from the EQ-5D instrument. It can also be obtained from the SF-6D score, which one may derive from the SF-36 questionnaire, using a validated method (Brazier et al., 2002).

The utility score analyses and consequent QALY calculations, as well as the Cost-Effectiveness model analyses will be further explained in a separate analysis plan provided by the HEOR R&D department.

## 6.7 Other Variables

Analysis Study Drug Taken (Yes / No)

A patient will be counted as dosed if any single dose was marked as taken in any of the Study Drug Administration (EX_X) forms, if there is a complete or partial date of 'last date of study medication' on the end of treatment page, or if study drug was dispensed and not all study drug was returned.

Analysis Date of First Dose

The Date of First Dose will be the Date of YM150/PTM Dose intake at baseline. In case of a missing/partial date, the earliest date compatible with the missing/partial date and compatible with being on the same day or later than the randomization date will be taken. This imputation should only be performed for subjects where the Analysis Study Drug Taken flag is yes.

Analysis Date/Time of First Dose

The Date and Time of First Dose will be the Date and Time of YM150/PTM Dose intake at baseline. In case of a missing/partial date, the earliest date compatible with the missing/partial date and compatible with being on the same day or later than the randomization date will be taken. In case of missing time, the analysis time of the first dose will be assumed to be 10 am.

Analysis Date of Last Dose

The Date of Last Dose will be collected on the End of Treatment Form. In case of a missing date, the date of the visit date of the End of Treatment visit will be taken.

If the date of last dose is partial, then the last date consistent with the information provided (e.g. last day of month or last day of year) will be used, unless this is after the date in the previous paragraph.

Note that the last dose, the treatment period and compliance are calculated including periods of dose interruption in the treatment period. Dose interruptions will be listed.

Analysis Visits

For the analysis of vital signs, ECG parameters and central laboratory parameters the visit variable as collected in the CRF will be used (i.e. no visit windows are used). Only in the case of a missing value for the eCRF baseline visit, will the last available value before randomization (e.g. from the screening visit) be taken for the analysis visit variable.

On Treatment Flag

For safety variables when the worst (maximum or minimum depending on the variable) value on study treatment is defined, the maximum or minimum will be calculated using only values measured from the analysis date of first double blind dose until the analysis date of last double blind dose. In case of assessments with missing dates the value will be regarded on double-blind treatment if it was collected from Visit 3 to end of treatment visit.

Post-Baseline Flag

For safety variables when the worst (maximum or minimum depending on the variable) value post-baseline is defined, the maximum or minimum will be calculated using only values from Visit 3 up to EOT/VD visit. For unscheduled assessments the value will be used if the assessment date is between the date of first dose and the day after the date of last dose.

Duration of Exposure to Double-blind Treatment Phase (weeks)

For each patient, the length of time on double-blind treatment will be calculated in weeks, using the following formula:

[(Date of last dose - Date of first dose) + 1] / 7

Time from Index Event to First Double Blind Dose

For each patient, the time from when the patient presented with the index event to first dose of study medication will be calculated in days, using the following formula:

Analysis Date of first DB dose - Date of index event

Percent Compliance

YM150/YM150 PTM tablet compliance until discontinuation of the study drug will be examined for patients in the safety population. The number of tablets which should have been taken will be assumed to be duration of DB exposure × 3 capsules per day :

$$\frac{\text{Total number of YM150/YM150 PTM tablets consumed in the investigational period}}{\text{Duration of DB exposure x 3}} \times 100$$

where:

- the total number of tablets consumed will be calculated as the difference between the total number of tablets dispensed and the total number of tablets returned.

For patients lost to follow up, the number of returns will be assumed to be zero.

Summaries of compliance will omit subjects only in the study for a short time, as the calculated compliance is misleading and not representative – especially if subjects failed to return study medications. More details will be in the TLF specifications

Prior and Concomitant Medications

Details on prior and concomitant medication use will be captured on the eCRF, including details of frequency, dose, route and indication.

Prior medications will be defined to be any medications taken prior to the first administration of the study treatment. Any medications which started prior to first administration of the study drug but which are ongoing during the study period will be defined to be both a prior and concomitant medication.

Concomitant medications will be included if they were taken between the day of first dose and the day of last dose. Medications ending on the day of first dose, or starting on the day of last dose will not be included. For partial start / end dates, the longest possible time consistent with the dates will be assumed.

Non-medication therapies will be similarly defined.

Prohibited and restricted medications taken at any time during the study will be determined as per the definitions in Section 7.2.4. At the BDRM each occurrence will be reviewed on a case-by-case basis to determine exclusion from the PPS.

Demographic and Baseline Characteristics

Inclusion and exclusion criteria at Screening, together with the review of the patient's inclusion/exclusion criteria and eligibility at Visit 2 will be recorded as a yes/no variable for each criterion. The patient's date of informed consent will also be documented.

Demographic characteristics will be recorded at the Screening, and will include month and year of birth, age, sex and race. Height and weight will also be recorded at Baseline (and weight recorded at EOT/VD as a vital sign). Each patient's body mass index (BMI) will be calculated as:

$$\text{BMI } (kg/m^2) = \frac{Weight(kg)}{\left[Height(m)\right]^2}$$

where the patient's height will be converted from cm into m by dividing by 100 first.

Substance use will be recorded at the Screening visit. Tobacco and alcohol use will be recorded, i.e. whether the patient is a current, former or non-user. Alcohol use will also detail type and number of units the patient consumes each week.

Diagnosis of ACS will be recorded which will include documenting the history of ACS and the details of acute management of the index event, classified as ST-Elevation Acute Coronary Syndrome (STE-ACS) or Non-ST-Elevation Acute Coronary Syndrome (NSTE-ACS).

**ST-Elevation Acute Coronary Syndrome (STE-ACS)**

- Signs and symptoms typical for myocardial ischemia lasting for more than 20 minutes at rest,
- Elevated cardiac enzymes (CK-MB, troponin-T, troponin-I) > 2xULN for CK-MB or > ULN for troponin on at least one occasion.
- One of the following:
  - ST-segment elevations of 1 mm or higher in two or more contiguous ECG leads,
  - New or presumably new left bundle branch block.

**Non-ST- Elevation Acute Coronary Syndrome (NSTE-ACS)**

- Signs and symptoms typical for myocardial ischemia lasting for more than 10 minutes at rest,
- Elevated cardiac enzymes (CK-MB, troponin- T, troponin-I) > 2xULN for CK-MB or > ULN for troponin on at least one occasion.

In addition, details will be recorded on procedures performed for the index event:

- Angiography,
- PCI,
- CABG.

The following will also be recorded at presentation of the index event:

- Did the patient have Congestive Heart Failure (CHF)?
- Killip class:
  - Class I (no CHF),
  - Class II (rales and/or JVD),
  - Class III (Pulmonary edema),
  - Class IV (Cardiogenic shock).
- Cardiac arrest?
- ST segment deviation?
- ST segment depression?
- Past history of MI prior to index event?
- Cardiac Arrest at any subsequent time during the hospital stay, but before randomization?
- Any episodes of Atrial Fibrillation during the hospital stay, but before randomization?
- Family history of coronary artery disease?
- Does the patient have a physically inactive lifestyle?
- Is the patient known to have multivessel coronary artery disease?
- Was revascularisation indicated, but impossible due to the extent of the disease, e.g. disease in small vessels?
- Did the patient have Congestive Heart Failure (CHF) after admission / at discharge?
- Were the cardiac enzymes elevated in the first sample drawn following the presentation?

Medical history will be recorded if present, along with an onset date, whether the condition is ongoing or a resolution date. Specific conditions of interest will also be checked.

The Global Registry of Acute Coronary Events (GRACE) risk score will be calculated at presentation of the index event and at discharge using the methods described in Appendix 3: GRACE risk score.

At the EOT/VD visit, an end of treatment eCRF page will be completed. Whether the patient completed treatment, the primary reason for premature discontinuation and date of last dose of study medication will be recorded. At the EOS visit, an end of study form will also be completed recording whether the patient completed the study, the primary reason for withdrawal and date of withdrawal.

# 7 STATISTICAL METHODOLOGY

## 7.1 General Considerations

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum and maximum, 25 % and 75 % percentiles. In addition for the PK parameters, the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories (with the exception of AEs) will be based on the number of patients with no missing data, i.e. will add up to 100 %. Unless otherwise stated, summaries will include columns for each treatment dose group, overall, YM150 dosing frequency, total YM150 daily dose and YM150 total:

**Table 5 Treatment Columns for Summaries**

| Groups | Label |
|---|---|
| Group 1 | YM150 5 mg bid |
| Group 2 | YM150 10 mg qd |
| Group 3 | YM150 15 mg bid |
| Group 4 | YM150 30 mg qd |
| Group 5 | YM150 30 mg bid |
| Group 6 | YM150 60 mg qd |
| Group 7 | Placebo |
| Groups 1 to 7 | Grand Total |
| Groups 1, 3 and 5 | YM150 bid |
| Groups 2, 4 and 6 | YM150 qd |
| Groups 1 and 2 | YM150 10 mg/day |
| Groups 3 and 4 | YM150 30 mg/day |
| Groups 5 and 6 | YM150 60 mg/day |
| Groups 1 to 6 | YM150 Total |

Output may be split across 2 pages, if possible in a logical manner (e.g. with Groups 1 to 7 separately on the first page and composite groups on the second page), ordered as above.

For any summaries by treatment visits, the data will be displayed as recorded on the eCRF page for that visit – no visit windows will be defined or used in the analyses.

Summaries of the follow-up period, the output will also be summarized as above (i.e. based on the treatment received in the double-blind treatment period).

All statistical comparisons will be made using two sided tests at the $\alpha$=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided. There will be no adjustments for multiplicity; therefore, there will need to be some caution in interpreting tests.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher on a Unix platform. Listings will be by investigator number, patient number and visit where the patient number (combining center number with screening number) will be used as the unique patient identifier.

## 7.2 Study Population

### 7.2.1 Disposition of Patients

The number and percentage of screened patients; that discontinue before randomization and that were randomized will be summarized for all screened patients. Screened patients who have not entered any further into the study will be identified via a completed screening failure log. In addition, the following patient data will be summarized and presented for each treatment grouping (Table 5):

- Number and percentage of randomized patients and number in each analysis set.
- Number and percentage of patients at each country and center, and for all centers combined for SAF.
- Number and percentage of patients excluded from PPS by reason for exclusion; and
- Number and percentage of patients who completed and prematurely discontinued from the double-blind treatment period, by reason for discontinuation for the SAF.
- Number and percentage of patients who completed and prematurely discontinued from the study, by reason for discontinuation for the SAF.

Listings will be produced of patients who discontinued prior to randomization. The date of discontinuation and reason for discontinuation will be listed. Separate listings will also be produced of all patients withdrawing during the double-blind treatment period, and the follow-up treatment period.

### 7.2.2 Protocol Violations

The definitions of protocol violations for the PPS and for reporting are those defined in Section 5.2.1 of the SAP, and are not related to the definitions used for site monitoring.

- Major protocol violations leading to exclusion from the PPS will be summarized by each treatment grouping (Table 5).
- Deviations from inclusion and exclusion criteria at screening will be listed, together with deviations from eligibility at baseline (does the patient still meet inclusion / exclusion criteria).
- Prohibited medications are listed.

All violations will be listed in the by-patient listings.

### 7.2.3 Demographic and Other Baseline Characteristics

Demographic characteristics (gender and age) will be summarized using descriptive statistics, for all screening failures (patient who signed the informed consent but were not randomized).

Demographic and other baseline characteristics will be summarized using descriptive statistics, by each treatment grouping (Table 5) for the SAF.

Descriptive statistics (without quartiles) for age, weight, BMI and height at study entry will be presented. Frequency tabulations for sex and race will be presented. Social history (alcohol and smoking habits), i.e. whether the patient is a current, former or non user will also be summarized by counts and percentages.

The classification of the primary diagnosis of ACS (i.e. STE-ACS and NSTE-ACS) will be summarized by each treatment grouping (Table 5).

The GRACE score at discharge and at presentation will be summarized by each treatment grouping (Table 5).

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) by each treatment grouping (Table 5) for the SAF only. Occurrence of the specific medical conditions.

- Congestive Heart Failure;
- Hypertension;
- Diabetes Mellitus;
- Stroke;
- Transient Ischemic Attacks (TIA);
- Acute Coronary Syndrome (ACS);
- Coronary Artery Bypass Graft (CABG);
- Percutaneous Coronary Intervention (PCI) (Coronary Angioplasty OR Percutaneous Transluminal Coronary Angioplasty (PTCA));
- Coronary Artery Disease (CAD);
- Peripheral Arterial Occlusive Disease (PAOD);
- Gilbert's Syndrome;
- Crigler-Najjar Syndrome;
- Liver Cirrhosis;
- Hepatic Insufficiency;
- Previous History of Major Bleeding

will be summarized for the SAF. A further table of medical history will be produced for those conditions which are ongoing at the start of the study.

All baseline data will be listed by investigator number and patient number.

### 7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DRL, and will be summarized by therapeutic subgroup and Anatomical Therapeutic Chemical (ATC) subgroup (levels 2 and 4) by each treatment grouping (Table 5) for the SAF. Concomitant medications will be included in all periods that they were taken in.

As with previous medication, concomitant medication will be summarized for each treatment grouping (Table 5Table 5) by therapeutic subgroup and chemical subgroup (ATC levels 2 and 4) for the SAF. Patients taking the same medication multiple times will be counted once per medication in each investigational period.

Non-medication therapies will be listed only.

A further table will be produced of prohibited and restricted medications in the treatment period. These will be identified as any of the medications in Appendix 1 [List of Excluded and Restricted Previous and Concomitant Medication], and will be summarized for the SAF.

All previous and concomitant medications will be listed separately by investigator number and patient number. On the concomitant medication listing flags for concomitant ASA and clopidogrel use, prohibited medications and restricted medications will be provided. Medications commencing in the follow-up period will also be listed separately.

## 7.3 Study Drugs

### 7.3.1 Extent of Exposure

Duration of exposure will be summarized using descriptive statistics and presented by treatment grouping (Table 5).

### 7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for patients in the SAF.

Percent overall YM150/YM150 PTM tablet compliance will be summarized by treatment grouping (Table 5) in two ways for the SAF:

- Descriptive statistics will be presented.
- Percent compliance will be categorized according to the following categories:
  - less than 50 %,
  - at least 50 %, less than 80 %,
  - at least 80 %, less than 90 %,
  - at least 90 % to less than or equal to 110 % ,
  - greater than 110 % to less than or equal to 125%
  - Unknown.
- Number and percentage of compliant patients (at least 80 % to less than or equal to 125 %).

Clopidogrel and ASA dosing will also be summarized

## 7.4 Analysis of Efficacy

### 7.4.1 Analysis of Primary Variable(s)

The primary endpoint for this study is not an efficacy variable but the incidence of adjudicated Ruby-1 modified ISTH major and non-major clinically relevant bleeding events. These data will be analyzed as described in Section 7.5.1.

### 7.4.2 Analysis of the Adjudicated Efficacy Events

The number of patients experiencing each of the efficacy related events and subcategories defined in Sections 6.1.1 and 6.1.2 will be summarized by treatment grouping (Table 5) both during the DB treatment period (only counting events on-treatment) and during the entire study period (counting also events after DB treatment). This will be presented for patients in the Full Analysis Set and repeated for patients in the Per-Protocol Set.

If a patient has more than one event of a particular type / for an endpoint, only the first occurrence of the event will be counted.

The cumulative risk (both at day 30 and at month 6), and 95% confidence limits, for each of the 3 composite efficacy related events defined in Sections 6.1.2 will be presented by treatment grouping (Table 5), using Kaplan-Meier estimates.

The estimated cumulative risk function versus time, using Kaplan-Meier estimates, will be plotted by treatment grouping (Table 5). All mentioned estimates will also be presented by stratifying for standard antiplatelet treatment (Clopidogrel or No Clopidogrel).

In addition, an inferential analysis similar to the analysis explained for the primary variable in section 7.5.1.1 (Cox regression model) will be performed for these 3 composite efficacy endpoints defined in Section 6.1.2. All efficacy analyses will be performed on the FAS. In order to evaluate the robustness of the results, the same analyses will be performed on the PPS. Both Kaplan-Meier Analysis and Cox regression model will be performed using events during the DB treatment period (on-treatment approach). In case of a significant amount of event off treatment during the follow-up period these inferential analyses might be repeated of the entire study (ITT approach).

In order to assess the homogeneity of results in subpopulations, the above Cox regression model will be repeated for each subpopulation. Hazard ratios (HR) will be calculated and reported using a forest plot. The variables that will be used to define these subpopulations analyses are gender, age groups, ACS type, GRACE risk score groups at presentation and discharge, previous ACS (<12 months), history of ischemic stroke or TIA, history of diabetes, myocardial revascularization or PCI performed as apart of the initial management.

### 7.4.3 Other Efficacy Variables

The total duration of hospitalization will be summarized using standard summary statistics.

Analysis of Patient Reported Outcomes

EQ-5D and SF-36 will be summarized descriptively overall and by treatment. Utility scores and analyses of the different domains in the EQ-5D, as well as the SF-36 questionnaires will be further explained in a separate document, provided by the HEOR R&D department.

#### 7.4.3.1 EQ-5D

The EQ-VAS will be summarized at baseline and EOT (V-D) using descriptive statistics. Change from baseline to each treatment visit and EOT in the EQ-VAS will also be summarized using descriptive statistics.

EQ-VAS will be inferentially analyzed at the EOT visit using an analysis of covariance model including standard antiplatelet treatment (Clopidogrel or No Clopidogrel) and treatment as class variables and baseline EQ-VAS as a covariate. The difference of means and their 95 % confidence intervals (CI) will be presented for each comparison of interest below:

**Table 6 Comparisons of Interest**

| Regimen | YM150 | | | | | | Placebo |
|---|---|---|---|---|---|---|---|
| | 5 mg bid | 10 mg qd | 15 mg bid | 30 mg qd | 30 mg bid | 60 mg qd | |
| Group | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| a) Increase for increasing dose by 10 mg | -0.053279 | -0.053279 | 0.004098 | 0.004098 | 0.090164 | 0.090164 | -0.081967 |
| b) Increase for a doubling in dose | -0.204526 | -0.204526 | 0.028691 | 0.028691 | 0.175835 | 0.175835 | 0 |
| c) bid – qd | 1/3 | -1/3 | 1/3 | -1/3 | 1/3 | -1/3 | 0 |
| d) 30 mg - 10 mg daily dose | -0.5 | -0.5 | 0.5 | 0.5 | 0 | 0 | 0 |
| e) 60 mg - 10 mg daily dose | -0.5 | -0.5 | 0 | 0 | 0.5 | 0.5 | 0 |
| f) Group 1 – 7 | 1 | 0 | 0 | 0 | 0 | 0 | -1 |
| g) Group 2 – 7 | 0 | 1 | 0 | 0 | 0 | 0 | -1 |
| h) Group 3 – 7 | 0 | 0 | 1 | 0 | 0 | 0 | -1 |
| i) Group 4 – 7 | 0 | 0 | 0 | 1 | 0 | 0 | -1 |
| j) Group 5 – 7 | 0 | 0 | 0 | 0 | 1 | 0 | -1 |
| k) Group 6 – 7 | 0 | 0 | 0 | 0 | 0 | 1 | -1 |

ANCOVA modeling will be performed in SAS 9.1.3 using PROC GLM, with a derivative of the code below with the relevant comparison:

```
proc glm data=ancova;
      class treatment prior_ac;
      by visit;
      model chngbas= base treatment antiplatelet /alpha=0.05 clparm;
      estimate ' e) Group 1 –7 ' treatment 1 0 0 0 0 0 -1;
run;
```

Normality tests will be performed on the absolute change from baseline to check that the normality assumption holds for ANCOVA. The assumptions will also be tested graphically by residual plots, Q-Q and other relevant plots. If the assumptions do not hold, a stratified rank ANCOVA will be considered.

#### 7.4.3.2 SF-36

The overall score of the SF-36, the scores on the physical health and mental health composite summary measures, and the score for the 8 sub domains, will be summarized at baseline and at EOT/VD visit using descriptive statistics. Change from baseline to EOT will be summarized using descriptive statistics.

The change from baseline to EOT in the overall score of the SF-36 will be analyzed using analysis of covariance, including standard antiplatelet treatment (Clopidogrel or No Clopidogrel) and treatment group as class variables and baseline score as covariate. The difference of means and their 95 % confidence intervals (CI) will be presented for each comparison of interest as above.

## 7.5 Analysis of Safety

The SAF analysis set will be used for all analyses of safety variables.

### 7.5.1 Analysis of the Primary Variable - Bleeding Adverse Events

#### 7.5.1.1 Primary Analysis of the Primary Variable

The primary endpoint of this study is the incidence of the following adjudicated events using the Ruby-1 modified ISTH definition at six months:

- major bleeding events,
- clinically relevant non-major bleeding events.

In this section, "event" means any one of the above and "incidence" means the presence/absence of the event combined with the time of the first event or time of censoring. The term "cumulative risk" refers to 1 – Kaplan-Meier survival estimate in a time to event analysis, for a particular time point. The primary analysis will analyze the first occurrence of the event – it will not distinguish between types of events.

The primary analysis will be based on the SAF analysis set – which defines evaluability for the primary analysis – all patients in the SAF will be evaluable, and be included in the primary analysis.

The primary hypothesis will be:

$H_0$: $\tau_{\text{Group A}} = \tau_{\text{Group B}}$ versus
$H_A$: $\tau_{\text{Group A}} \neq \tau_{\text{Group B}}$

Where $\tau$ is the cumulative risk of major bleed and CRNM bleeding events at month 6. Group A and Group B will vary depending on the comparison of interest (Table 6).

The number of patients experiencing an event will be summarized by treatment grouping (Table 5). The cumulative risk and 95 % CIs at 30 days and at 6 months will be calculated using Kaplan-Meier estimates.

The estimated cumulative risk function versus time, using Kaplan-Meier estimates, will be plotted by treatment grouping (Table 5). All mentioned estimates will also be presented by stratifying for standard antiplatelet treatment (Clopidogrel or No Clopodogrel).

This primary variable will also be inferentially analyzed using a Cox regression model. The model will include terms for treatment group and standard antiplatelet treatment (Clopidogrel or No clopidogrel). The SAS procedure will be similar to the following, including all relevant comparisons of interest:

```
ods output type3=type3;
proc tphreg data=data;
     class treatment antiplatelet / param=glm;
     model time_to*event(1)= treatment antiplatelet / risklimits
     ties=discrete;
     id patient;

     contrast "a) Increase for adding 10 mg of YM150"
     treatment -0.053279  -0.053279  0.004098 0.004098 0.090164
     0.090164  -0.081967 / est;

     contrast "b) Increase for doubling dose"
     treatment -0.204526  -0.204526  0.028691  0.028691  0.175835  0.175835
     0 / est;

     contrast "c) bid - qd" treatment 0.33 -0.33 0.33 -0.33 0.33 -0.33 0
     /est;
     contrast "d) 30 mg - 10 mg" treatment -0.5 -0.5 0.5 0.5 0 0 0 /est;
     contrast "e) 60 mg - 10 mg " treatment -0.5 -0.5 0 0 0.5 0.5 0 /est;
     contrast "f) Group 1 – 7" treatment 1 0 0 0 0 0 -1 /est;
     contrast "g) Group 2 – 7" treatment 0 1 0 0 0 0 -1 /est;
     contrast "h) Group 3 – 7" treatment 0 0 1 0 0 0 -1 /est;
     contrast "i) Group 4 – 7" treatment 0 0 0 1 0 0 -1 /est;
     contrast "j) Group 5 – 7" treatment 0 0 0 0 1 0 -1 /est;
     contrast "k) Group 6 – 7" treatment 0 0 0 0 0 1 -1 /est;
run;
```

P-values (calculated from Type 3 Wald chi-squared tests) will be presented for the overall effects of including treatment and standard antiplatelet treatment (Clopidogrel or No Clopidogrel) in the model. Hazard ratios will be presented for the comparisons of interest as stated in Table 6 along with their 95 % confidence intervals.

There will be no adjustment for multiplicity in the tests. This is a Phase 2 study for dose and regimen selection; each test will be used as part of the information for selecting the appropriate dose for Phase 3.

As a sensitivity analysis the above analyses will also be repeated based on the PPS.

The proportional hazards assumption will be verified graphically using a log-cumulative hazard plot against log-survival time. This plot will give approximately parallel lines if the proportional hazards assumption between treatment subgroups holds.

#### 7.5.1.2 Secondary Analysis of the Primary Variable

The analyses of the primary variable will be repeated including country in the model as a fixed effect if the number of events allows. Countries may be pooled if the number of events is low; Countries will be used unless alternative pooling is specified at the BDRM, based on numbers of patients by site and country. The interaction between treatment and country will

also be investigated. The analyses of the primary variable will also be repeated including time from Index Event to the analysis date of first dose as a covariate.

In order to assess the homogeneity of results in subpopulations, the above Cox regression model will be repeated for each subpopulation. Hazard ratios (HR) will be calculated and reported using a forest plot. The variables that will be used to define these subpopulations analyses are gender, age groups, ACS type, GRACE risk score groups at presentation and discharge, previous ACS (<12 months), history of ischemic stroke or TIA, history of diabetes, myocardial revascularization or PCI performed as apart of the initial management.

### 7.5.2 Incidence of other bleedings

For all secondary safety events described in section 6.2.2, the cumulative risks and cumulative risk function versus time at 30 days and at 6 months will be produced in the same way as described in section 7.5.1.1.

In addition, an inferential analysis similar to the analysis explained for the primary variable in section 7.5.1.1 (Cox regression model) will be performed for these secondary safety endpoints.

Both Kaplan-Meier Analysis and Cox regression model will be performed using events during the DB treatment period (on-treatment approach). In case of a significant amount of event off treatment during the follow-up period these inferential analyses might be repeated for the entire study (ITT approach).

All bleeding adverse events will be listed.

The blood transfusion log will be listed by investigator number and patient only.

### 7.5.3 Adverse Events

Adverse events with onset before the start of treatment will be listed but will not be tabulated. In addition, all adverse events for randomized patients that do not belong to SAF will be listed but not tabulated. All AEs and Serious Adverse Events (SAEs) will be listed for individual patients, along with information regarding onset, duration, severity, and relationship to study drug.

For tables of severity the worst severity will be taken. AEs with unknown severity will be included as severe. A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship. If an adverse event changes in severity or relationship, then the adverse event will be counted only once with the worst severity and highest degree of relationship.

The following overall summaries will be tabulated:

- Number and percentage of patients with TEAEs,
- Number of TEAEs,
- Number and percentage of patients with drug related TEAEs,
- Number of drug related TEAEs,

- Number of deaths,
- Number and percentage of patients with treatment emergent SAEs,
- Number of treatment emergent SAEs,
- Number and percentage of patients with drug related SAEs,
- Number of drug related SAEs,
- Number and percentage of patients with TEAEs leading to permanent discontinuation of the study treatment,
- Number of TEAEs leading to permanent discontinuation of the study treatment,
- Number and percentage of patients with drug related AEs leading to permanent discontinuation of the study treatment,
- Number of drug related AEs leading to permanent discontinuation of the study treatment,
- Number and percentage of patients with TEAEs by severity,
- Number of TEAEs by severity,
- Number and percentage of patients with drug related TEAEs by severity,
- Number of drug related TEAEs by severity,
- Number and percentage of patients with hepatic AEs (see Appendix 2: Hepatic Adverse Events),
- Number of hepatic AEs (see Appendix 2: Hepatic Adverse Events).

The coding dictionary for this study will be MedDRA version 9.1. It will be used to summarize AEs by system organ class (SOC) and preferred term.

The following tables will also be produced by SOC and preferred term:

- Table of patients with TEAEs by SOC and preferred term,
- Table of patients with drug related TEAEs by SOC and preferred term,
- Table of patients with SAEs by SOC and preferred term,
- Table of patients with AEs leading to treatment discontinuation by SOC and preferred term,
- Table of patients with hepatic AEs (see Appendix 2: Hepatic Adverse Events) by SOC and preferred term,
- Table of events occurring in greater than or equal to 10% in any treatment dose group,
- Table of events occurring in greater than or equal to 2% in any treatment dose group,
- Table of the incidence and number of treatment emergent adverse events by severity.

The following will be listed:

- Pre-treatment AEs (before first study treatment) and all AEs (with a flag to identify those which are treatment emergent),
- SAEs,
- AEs leading to discontinuation,
- Hepatic AEs (see Appendix 2: Hepatic Adverse Events),
- Deaths,
- Adverse events occurring in patients not in the Safety Analysis Set.

### 7.5.4 Clinical Laboratory Evaluation

Clinical laboratory data (hematology, chemistry and urinalysis) will be listed including central and local results. Central laboratory results will be used in summary tabulations.

Clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum, quartile 1, quartile 3 and median for each treatment grouping (Table 5) at each visit. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline measurement, this will be summarized for each treatment visit. For each quantitative laboratory parameter, a graph will be created displaying the median value (shown as times ULN in the log scale) by treatment group versus visit.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges and will be summarized using standard summary statistics. In addition, summary statistics will be presented for each laboratory parameter range defined in Section 6.2.7.

Shift tables of changes in classification from baseline to EOT/ V-D will be displayed. A further shift table will be presented presenting the changes in classification from Baseline to the worst double-blind treatment value.

Abnormal laboratory measurements at each visit will be listed for all patients.

The decrease in hemoglobin for any patients experiencing a bleeding event will be calculated and summarized using standard summary statistics. The table will be split by first occurrence of bleeding event, second occurrence etc. in order to capture any patients who experience more than one event.

A listing of hemoglobin results for patients where a local laboratory has been used will be produced.

#### 7.5.4.1 Hepatic parameters

Liver laboratory abnormalities (ALT, AST, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, alkaline phosphatase and Gamma-Glutamyl Transferase (γGT), values, changes from baseline and percentage changes from baseline (Total Bilirubin, Direct Bilirubin and Indirect (Bilirubin only) will be summarized by treatment grouping (Table 5) and scheduled visit. The peak value will be summarized for these parameters.

Graphs for ALT, AST and Bilirubin will be produced showing the ALT, AST and Bilirubin (shown as times ULN on the log scale) versus time for patients with a marked liver abnormality. Each patient will have a separate line on the graph.

For ALT, AST and Total Bilirubin, the worst value is the highest value. All samples post-baseline during the double-blind treatment will be included. Summaries will also be produced by treatment grouping (Table 5) for the whole study using the worst value. The following will be summarized:

- The number of patients with moderate and marked liver abnormality:

- Moderate liver abnormality is defined as Total Bilirubin >2 x ULN, ALT > 3 x ULN, and / or AST > 3 x ULN
- Marked liver abnormality is defined as Total Bilirubin >3 x ULN, ALT > 5 x ULN, and / or AST > 5 x ULN;
  Or Total Bilirubin > 2 x ULN with ALT or AST > 3 x ULN

A table will be produced with the number and percentage of patients with

- ALT > 3, > 5, > 10, >20 x ULN,
- AST > 3, > 5, > 10, >20 x ULN,
- ALT or AST > 3, > 5, > 10, >20 x ULN,
- ALP > 1.5 x ULN,
- Total Bilirubin >1.5, >2, >3 and >5 x ULN,
- Total Bilirubin > 2 x ULN concurrent with ALT or AST > 3 x ULN.

There will also be a listing of AST, ALT, γGT, ALP, total bilirubin, indirect bilirubin and direct bilirubin for patients who had marked liver abnormalities. A separate listing will be produced for patients with moderate or marked liver abnormalities, and those with total bilirubin > 2 x ULN and ALT or AST > 3 x ULN at any time point.

Peak ALT versus peak Total Bilirubin (log scales) will be plotted, with one observation for each patient. Treatment group will be identified by different plotting symbols. The peaks are calculated for each patient for all values after the start of treatment. An additional graph will also be created for the AST value versus Peak Total Bilirubin.

For patients with marked liver abnormalities, an individual plot of ALT, AST and Total Bilirubin (as a ratio of the ULN) by time, with vertical lines for the start and end of study treatment will be produced.

Hepatic monitoring visits as described in Section 6.2.11 will be listed only.

#### 7.5.4.2 Renal parameters

A table will be produced by treatment grouping (Table 5) and visit, summarizing the number and percentage of patients with the following elevated renal biomarkers abnormalities:

- Increase of serum creatinine > 25 % and > 50 % compared to baseline serum creatinine,
- Increase of scheduled serum creatinine > 25 % and > 50 % compared to previous scheduled visit serum creatinine,
- Increase of serum creatinine >1.5, >2 ULN.

There will also be a listing of patients with an increase in serum clearance. Renal monitoring visits as described in Section 6.2.12 will be listed only.

### 7.5.5 Vital Signs

Vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate and weight] will be summarized using mean, standard deviation, minimum, maximum, quartile 1, quartile 3 and median by treatment grouping (Table 5) and visit. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline measurement and summarized by treatment grouping (Table 5) and visit.

The number and percentage of patients in each of the categories listed below will be summarized at each visit, for the worst value during the DB treatment period and the worst value post-baseline during the study:

- Systolic Blood Pressure <90 mmHg,
- Systolic Blood Pressure >140 mmHg,
- Diastolic Blood Pressure <40 mmHg,
- Diastolic Blood Pressure >90 mmHg,
- Pulse Rate <60 bpm,
- Pulse Rate >90 bpm,

All vital sign data will be listed including the derived data categories the patient is in.

### 7.5.6 Physical Examination Findings

Number and percent of patients with normal and abnormal findings for each body system of physical examination will be tabulated at each visit.

### 7.5.7 Electrocardiograms (ECGs)

The listings will present both investigator and central assessments.

ECG variables from the central reading will be summarized using mean, standard deviation, minimum, maximum, quartile 1, quartile 3 and median for each treatment grouping (Table 5) at each visit, including changes from baseline. For quantitative variables changes from Baseline will also be summarized using standard summary statistics.

For the investigator assessments, number and percent of patients with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12 lead ECG will be tabulated by treatment grouping (Table 5) at each visit, and for the worst status post-baseline during the study.

For the central assessment, the number and percent of patients with normal and abnormal, and the number and percentage of patients with each type of abnormality will be presented for each visit, for baseline and for “any post-baseline assessment”.

### 7.5.8 Pregnancies

A detailed listing of all pregnancies will be provided.

### 7.5.9 Other Safety-Related Observations

Details from the mortality report, diagnostic imaging and Rankin index will be listed only.

## 7.6 Analysis of PK and/or PD

PK and PD parameter estimates supplied will be summarized by treatment grouping (Table 5) in a separate report.

The plasma concentration data will be subjected to population PK analysis. The aim of this analysis is to develop a compartmental model of YM-222714 plasma concentration vs. time profiles, taking into account inter-patient and intra-patient (if possible) variability in YM-222714 PK. In addition, the effects of selected covariates on the clearance will be evaluated, e.g. sex, age, race, body size.

Information regarding the pharmacokinetic analysis will be described in the separate PK analysis plan. The results and the model development will be described in detail in a separate population PK report.

## 7.7 Other Analyses

Not applicable

## 7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

Ongoing review of safety data will be completed by an independent DSMB. The frequency of the DSMB meetings is determined by the DSMB, and depends on factors such as patient recruitment, the frequency and nature of SAEs, any potential safety signals, etc. The DSMB will review all safety data relating to bleeding complications, thromboembolic events, important cardiac events, important renal events and important hepatic events. Statistical analysis may be performed for the DSMB, but is further documented in the DSMB charter, statistical analysis plan and tables manual.

## 7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Refer to the PK / PD analysis plan for details of the handling of PK and PD parameters.

### 7.9.1 Missing Data

The handling of missing values and evaluability is specified for the various endpoints. In general no imputation is performed, and the data is analyzed as observed.

### 7.9.2 Outliers

The data will be checked for outliers and unusual observations. All values will be included in the analysis.

### 7.9.3 Visit Windows

Observations will be analyzed as observed, and the analyses will use the visits as in the eCRF data. Thus unscheduled samples will not be included in analyses of specific windows / time-

points. Unscheduled samples will be included in periods covering more than one visit – such as minimum / maximum in the treatment period.

**Baseline:** If missing values for laboratory, ECG or vital sign parameters are present for the baseline visit in the CRF, the last available value before randomization (e.g. from the screening visit) will be taken for the analysis visit variable.

## 7.10 Changes from the protocol

- For the analysis of the Cox proportional hazards, a slightly different model will be set up so each treatment group (7 arms) will be included in the model as a categorical variable, and contrasts will be produced to estimate each hazard ratio required. Therefore, only one model will be used to obtain all hazard ratios.
- Classification of bleeding events: The protocol contains bleeding definitions that are similar, but not identicial to the traditional ISTH criteria. The definition in the protocol has therefore been termed "Ruby-1 modified ISTH criteria" and used as primary. The unmodified ISTH criteria are used as a secondary variable.
- The TIMI definitions have also been included as secondary variables. The TIMI definitions have been expanded to include extra categories TIMI requiring medical attention and TIMI insignificant bleeding.
- The sub-classification of deaths / MIs and stent thrombosis was added to the adjudication process on advice of the adjudication chair.

# 8 REFERENCES

(1) Cannon CP. American College of Cardiology Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes of Patients with acute Coronary Syndromes. J Am Coll Cardiol 2001; 7:2114-30.

(2) Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Gabriel Steg P, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A Validated Prediction Model for All Forms of Acute Coronary Syndrome. JAMA. 2004; 291:2727-2733.

(3) Granger CB, Goldberg RJ, Dabbous OH, Pieper KS, Eagle KA, Cannon CP, Van de Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. Arch Intern Med. 2003; 163:2345-2353.

(4) ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics).

(5) ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics).

(6) International Society on Thrombosis and Hemostasis (ISTH). (www.isth.org).

## 8.1 Appendix 1: List of Excluded and Restricted Previous and Concomitant Medication

[*Note: Material additional to the protocol is in italics within square brackets. WHO codes are generally matched using the first 6 digits – the other digits generally representing the salt and the brand - ????? represents any digits.*]

During the acute management of the index event several antithrombotics can and will be utilized as per standard of care. Patients can only be randomized to double-blind study drug, if they are clinically stable and there is no need anymore for antithrombotic treatment other then ASA and/or clopidogrel.

Antithrombotics need to be discontinued sufficiently in time prior to intake of the first dose of double-blind study drug, i.e.:

- Parenteral Unfractionated Heparin (UFH) need to be stopped at least 2 hours, *[Identified by Unfractionated heparin in CM1TRT in CRFDATA.CM_4]*
- Bivalirudin needs to be stopped at least 2 hours, *[WHO code 015068?????]*
- Low Molecular Weight Heparin (LMWH) need to be stopped at least 8 hours, *[Identified by Low molecular weight heparin in CM1TRT in CRFDATA.CM_4]*
- Fondaparinux need to be stopped at least 18 hours, *[WHO code 015512?????]*
- Glycoprotein (GP) IIb/IIIa antagonists need to be stopped
    - at least 12 hours for abciximab, *[Idenitified by Abciximab in CM1TRT in CRFDATA.CM_4 or WHO code 01273?????]*
    - at least 6 hours for eptifibatide or tirofiban. *[Idenitified by Eptifibatide or Tirofiban in CM1TRT in CRFDATA.CM_4 or WHO codes 013609????? And 013833????? respectively]*

*Medications will be classified as follows, in order from top to bottom (medications in a higher group will not be included in a subsequent group. A medication will be classified according to the first matching criteria, even if other codes for that same medication meet other criteria (for example ASA has multiple matching ATC codes).*

- *Medications classed as topical (route on the eCRF) will not be counted as protocol violations (not in any of the groups below)*
- *Clopidogrel (Loading dose of clopidogrel or maintenance dose of clopidogrel in the "Antiplatelet, anticoagulant, thrombolytic medication" eCRF page, or WHO code 012207?????. The WHO code should pick up all of these.*
- *Salicylic acid – WHO drug codes 000027?????, 000212?????, 000052?????, 08000?????*
- *Salicylic acid derivatives – Who codes 004130?????, 002749????? Or ATC codes*
    - *A07EC (Amino salicylic acid and similar agents),*
    - *D02AF (Salicylic Acid preparations) – Note this is in dermatological preparations;*

  - *J04AA (Amino salicylic acid and derivatives),*
  - *M02AC (Preparations with salicylic acid derivatives);*
  - *N02BA (Salicylic acid derivatives); and*
  - *P02DA (Salicylic acid derivatives).*
- *Anticoagulant agents (B01AA, B01AB, B01AE, B01AX):*
  - *B01AA Vitamin K antagonists;*
  - *B01AB Heparin group;*
  - *B01AE Direct thrombin inhibitors; and*
  - *B01AX Other antithrombotic agents*
- *Thrombolytics or Other antiplatelet agents*
  - *B01AC Antiplatelet agents; and*
  - *B01AD Thrombolytics*
- *NSAIDs (ATC codes M01A, M01B and S01BC, N02BB)*
  - Celecoxib (WHO code 014005?????)
  - Paracetamol (WHO code 000200?????)
  - Other NSAIDs *(ATC codes M01A, M01B and S01BC, N02BB)*

Subjects need to be on current standard antiplatelet therapy as per local guidelines defined as: ASA 75-325 mg daily (as per local guidelines use of the lowest possible dose, i.e. 75-81 mg daily, is recommended) alone or in combination with clopidogrel 75 mg daily or clopidogrel 75 mg alone.

Concomitant use of anticoagulants (e.g., vitamin K antagonists, UFH, LMWH, fondaparinux, antithrombins), other antiplatelet drugs (e.g., dipyridamole, cilostazol, prasugrel, ticlopidine), GP IIb/IIIa antagonists or fibrinolytics are not allowed during the double-blind study period. However, temporary use of appropriate antithrombotic medication will be allowed if blinded study drug is interrupted in order to perform PCI as described in Section 3.4 of the protocol.

Concomitant use of Non Steroidal Anti Inflammatory Drugs (NSAIDs) is not allowed during the double-blind study period. Celecoxib and paracetamol are allowed.

Subjects with a need for anticoagulant treatment for concomitant conditions (e.g., prosthetic heart valves) should not be randomized.

Digitalis derivatives (e.g., digoxin and digitoxin), quinidine, amiodarone, and methotrexate are allowed, but therapeutic drug monitoring is recommended as clinically indicated.

**EXAMPLES (Copied here for simply reference, the algorithm for determining categories is defined above)**

**Thrombolytics**

Alteplase, Ancrod, Anistreplase, Brinase, Drotrecogin alfa, Fibrinolysin, Protein C, Reteplase, Saruplase, Streptokinase, Tenecteplase, Urokinase *[B01A]*

**Antiplatelet agents**

Abciximab, Aloxiprin, Beraprost, Ditazole, Carbasalate calcium, Cilostazol, Cloricromen, Dipyridamole, Eptifibatide, Indobufen, Iloprost, Picotamide, Prasugrel, Prostacyclin, Ticlopidine, Tirofiban, Treprostinil, Triflusal *[B01AC]*

**Anticoagulants**

Vitamin K antagonist: Acenocoumarol, Clorindione, Dicumarol (Dicoumarol), Diphenadione, Ethyl biscoumacetate, Phenprocoumon, Phenindione, Tioclomarol, Warfarin *[B01AA]*

Heparin group: Antithrombin III, Bemiparin, Dalteparin, Danaparoid, Enoxaparin, Heparin, Nadroparin, Parnaparin, Reviparin, Sulodexide, Tinzaparin *[Included in B01AB Heparin group]*

Direct Thrombin Inhibitors: Argatroban, Bivalirudin, Desirudin, Hirudin, Lepirudin, Dabigatran *[B01AE]*

Others: Fondaparinux *[B01AX05]*, Defibrotide, Dermatan sulfate.

Antithrombotics need to be discontinued a sufficient amount of time before the first dose of double-blind study drug as indicated in Table 8.

Major protocol violations will be assessed on a case-by-case basis at the BDRM. Due to the length of the study, if considered appropriate at the BDRM, only a subset of the patients data may be removed from the PPS analyses. That is, data following violation of the above criteria may be removed from the PPS analyses, but all data collected prior to the violation will still be used in the PPS analyses. This might not be applicable for some specific major protocol violations where the whole patient might be removed from the PPS.

**Table 2 Minimum Time to have Elapsed from Discontinuation of Antithrombotic to First Intake of Study Drug**

| **Antithrombotic Medication** | **Minimum Elapsed Time from stopping Antithrombotic to First Dose of Study Drug (h)** |
|---|---|
| Parenteral Unfractionated Heparin (UFH) | 2 |
| Bivalirudin | 2 |
| Low Molecular Weight Heparin (LMWH) | 8 |
| Fondaparinux | 18 |
| Glycoprotein (GP) IIb/IIIa antagonists: abciximab | 12 |
| Glycoprotein (GP) IIb/IIIa antagonists: eptifibatide or tirofiban | 6 |
| Glycoprotein (GP) IIb/IIIa antagonists: tirofiban | 6 |
| Other antithrombotic medication (e.g. hirudin) | None |

Violation of these washout times will not be considered a Major Protocol Violation. Use of antithrombotic agents apart from ASA/clopidogrel after the first dose of study drug will be considered on a case-by case basis. In general, cumulative use of antithrombotics for >7 days between first and last dose of study drug will be considered a major protocol violation. Days on which study drug was interrupted will not be counted.

## 8.2 Appendix 2: Hepatic Adverse Events

Below is a list of preferred terms to include:

| Preferred Term Name | Preferred Term code |
|---|---|
| Bilirubin excretion disorder | 10061009 |
| Cholaemia | 10048611 |
| Cholestasis | 10008635 |
| Cholestatic liver injury | 10067969 |
| Cholestatic pruritus | 10064190 |
| Hepatitis cholestatic | 10019754 |
| Hyperbilirubinaemia | 10020578 |
| Icterus index increased | 10021209 |
| Jaundice | 10023126 |
| Jaundice cholestatic | 10023129 |
| Jaundice hepatocellular | 10023136 |
| Mixed liver injury | 10066758 |
| Ocular icterus | 10058117 |
| Yellow skin | 10048245 |
| 5'nucleotidase increased | 10000028 |
| Alanine aminotransferase abnormal | 10001547 |
| Alanine aminotransferase increased | 10001551 |
| Ammonia abnormal | 10001942 |
| Ammonia increased | 10001946 |
| Ascites | 10003445 |
| Aspartate aminotransferase abnormal | 10003477 |
| Aspartate aminotransferase increased | 10003481 |
| Bacterascites | 10068547 |
| Bile output abnormal | 10051344 |
| Bile output decreased | 10051343 |
| Bilirubin conjugated abnormal | 10067718 |
| Bilirubin conjugated increased | 10004685 |
| Biopsy liver abnormal | 10004792 |
| Blood alkaline phosphatase abnormal | 10059571 |
| Blood alkaline phosphatase increased | 10059570 |
| Blood bilirubin abnormal | 10058477 |
| Blood bilirubin increased | 10005364 |
| Blood bilirubin unconjugated increased | 10005370 |
| Blood cholinesterase abnormal | 10005429 |
| Blood cholinesterase decreased | 10005430 |
| Bromosulphthalein test abnormal | 10006408 |
| Caput medusae | 10007213 |
| Child-Pugh-Turcotte score increased | 10068287 |
| Foetor hepaticus | 10052554 |
| Galactose elimination capacity test abnormal | 10059710 |
| Galactose elimination capacity test decreased | 10059712 |
| Gamma-glutamyltransferase abnormal | 10017688 |
| Gamma-glutamyltransferase increased | 10017693 |

| Preferred Term Name | Preferred Term code |
|---|---|
| Guanase increased | 10051333 |
| Haemorrhagic ascites | 10059766 |
| Hepaplastin abnormal | 10019621 |
| Hepaplastin decreased | 10019622 |
| Hepatic artery flow decreased | 10068997 |
| Hepatic congestion | 10019645 |
| Hepatic enzyme abnormal | 10062685 |
| Hepatic enzyme decreased | 10060794 |
| Hepatic enzyme increased | 10060795 |
| Hepatic function abnormal | 10019670 |
| Hepatic hydrothorax | 10067365 |
| Hepatic mass | 10057110 |
| Hepatic pain | 10019705 |
| Hepatic sequestration | 10066244 |
| Hepatic vascular resistance increased | 10068358 |
| Hepatobiliary scan abnormal | 10066195 |
| Hepatomegaly | 10019842 |
| Hepatosplenomegaly | 10019847 |
| Hyperammonaemia | 10020575 |
| Hyperbilirubinaemia | 10020578 |
| Hypercholia | 10051924 |
| Hypertransaminasaemia | 10068237 |
| Hypoalbuminaemia | 10020942 |
| Kayser-Fleischer ring | 10023321 |
| Leucine aminopeptidase increased | 10024275 |
| Liver function test abnormal | 10024690 |
| Liver induration | 10052550 |
| Liver palpable subcostal | 10024704 |
| Liver scan abnormal | 10061947 |
| Liver tenderness | 10024712 |
| Mitochondrial aspartate aminotransferase increased | 10064712 |
| Molar ratio of total branched-chain amino acid to tyrosine | 10066869 |
| Oedema due to hepatic disease | 10049631 |
| Perihepatic discomfort | 10054125 |
| Periportal oedema | 10068821 |
| Peritoneal fluid protein abnormal | 10069000 |
| Peritoneal fluid protein decreased | 10068999 |
| Peritoneal fluid protein increased | 10068998 |
| Pneumobilia | 10066004 |
| Portal vein flow decreased | 10067337 |
| Portal vein pressure increased | 10064936 |
| Retinol binding protein decreased | 10048473 |
| Retrograde portal vein flow | 10067338 |
| Total bile acids increased | 10064558 |
| Transaminases abnormal | 10062688 |
| Transaminases increased | 10054889 |
| Ultrasound liver abnormal | 10045428 |

| Preferred Term Name | Preferred Term code |
|---|---|
| Urine bilirubin increased | 10050792 |
| Urobilin urine present | 10053125 |
| X-ray hepatobiliary abnormal | 10056536 |
| Acute hepatic failure | 10000804 |
| Anorectal varices | 10068924 |
| Anorectal varices haemorrhage | 10068925 |
| Ascites | 10003445 |
| Asterixis | 10003547 |
| Bacterascites | 10068547 |
| Biliary cirrhosis | 10004659 |
| Biliary cirrhosis primary | 10004661 |
| Biliary fibrosis | 10004664 |
| Cholestatic liver injury | 10067969 |
| Chronic hepatic failure | 10057573 |
| Coma hepatic | 10010075 |
| Cryptogenic cirrhosis | 10063075 |
| Duodenal varices | 10051010 |
| Gastric varices | 10051012 |
| Gastric varices haemorrhage | 10057572 |
| Hepatectomy | 10061997 |
| Hepatic atrophy | 10019637 |
| Hepatic calcification | 10065274 |
| Hepatic cirrhosis | 10019641 |
| Hepatic encephalopathy | 10019660 |
| Hepatic encephalopathy prophylaxis | 10066599 |
| Hepatic failure | 10019663 |
| Hepatic fibrosis | 10019668 |
| Hepatic hydrothorax | 10067365 |
| Hepatic infiltration eosinophilic | 10064668 |
| Hepatic lesion | 10061998 |
| Hepatic necrosis | 10019692 |
| Hepatic steatosis | 10019708 |
| Hepatitis fulminant | 10019772 |
| Hepatobiliary disease | 10062000 |
| Hepatocellular foamy cell syndrome | 10053244 |
| Hepatocellular injury | 10019837 |
| Hepatopulmonary syndrome | 10052274 |
| Hepatorenal failure | 10019845 |
| Hepatorenal syndrome | 10019846 |
| Hepatotoxicity | 10019851 |
| Liver and small intestine transplant | 10052280 |
| Liver disorder | 10024670 |
| Liver injury | 10067125 |
| Liver operation | 10062040 |
| Liver transplant | 10024714 |
| Lupoid hepatic cirrhosis | 10025129 |
| Mixed liver injury | 10066758 |

| Preferred Term Name | Preferred Term code |
|---|---|
| Nodular regenerative hyperplasia | 10051081 |
| Oedema due to hepatic disease | 10049631 |
| Oesophageal varices haemorrhage | 10030210 |
| Portal hypertension | 10036200 |
| Portal hypertensive enteropathy | 10068923 |
| Portal hypertensive gastropathy | 10050897 |
| Portal shunt | 10036204 |
| Portal triaditis | 10053218 |
| Portopulmonary hypertension | 10067281 |
| Renal and liver transplant | 10052279 |
| Retrograde portal vein flow | 10067338 |
| Reye's syndrome | 10039012 |
| Spider naevus | 10041519 |
| Subacute hepatic failure | 10056956 |
| Varices oesophageal | 10056091 |
| Acute graft versus host disease in liver | 10066263 |
| Autoimmune hepatitis | 10003827 |
| Chronic hepatitis | 10008909 |
| Cytolytic hepatitis | 10050904 |
| Granulomatous liver disease | 10018704 |
| Hepatitis | 10019717 |
| Hepatitis acute | 10019727 |
| Hepatitis cholestatic | 10019754 |
| Hepatitis chronic active | 10019755 |
| Hepatitis chronic persistent | 10019759 |
| Hepatitis fulminant | 10019772 |
| Hepatitis toxic | 10019795 |
| Ischaemic hepatitis | 10023025 |
| Liver sarcoidosis | 10068664 |
| Lupus hepatitis | 10067737 |
| Radiation hepatitis | 10051015 |
| Benign hepatic neoplasm | 10004269 |
| Focal nodular hyperplasia | 10052285 |
| Haemangioma of liver | 10018821 |
| Haemorrhagic hepatic cyst | 10067796 |
| Hepatic adenoma | 10019629 |
| Hepatic cyst | 10019646 |
| Hepatic cyst ruptured | 10053973 |
| Hepatic haemangioma rupture | 10054885 |
| Hepatic angiosarcoma | 10067388 |
| Hepatic cancer metastatic | 10055110 |
| Hepatic cancer stage I | 10059318 |
| Hepatic cancer stage II | 10059319 |
| Hepatic cancer stage III | 10059324 |
| Hepatic cancer stage IV | 10059325 |
| Hepatic neoplasm | 10019695 |
| Hepatic neoplasm malignant | 10019697 |

| Preferred Term Name | Preferred Term code |
|---|---|
| Hepatic neoplasm malignant non-resectable | 10019698 |
| Hepatic neoplasm malignant recurrent | 10019700 |
| Hepatic neoplasm malignant resectable | 10019701 |
| Hepatobiliary carcinoma in situ | 10061202 |
| Hepatobiliary neoplasm | 10061203 |
| Hepatoblastoma | 10062001 |
| Hepatoblastoma recurrent | 10019823 |
| Liver carcinoma ruptured | 10050842 |
| Malignant hepatobiliary neoplasm | 10061239 |
| Mixed hepatocellular cholangiocarcinoma | 10027761 |
| Antithrombin III decreased | 10049547 |
| Blood fibrinogen abnormal | 10005518 |
| Blood fibrinogen decreased | 10005520 |
| Blood thrombin abnormal | 10005818 |
| Blood thrombin decreased | 10005820 |
| Blood thromboplastin abnormal | 10005824 |
| Blood thromboplastin decreased | 10005826 |
| Coagulation factor decreased | 10009736 |
| Coagulation factor IX level abnormal | 10061770 |
| Coagulation factor IX level decreased | 10009746 |
| Coagulation factor V level abnormal | 10061771 |
| Coagulation factor V level decreased | 10009754 |
| Coagulation factor VII level abnormal | 10061772 |
| Coagulation factor VII level decreased | 10009761 |
| Coagulation factor X level abnormal | 10061774 |
| Coagulation factor X level decreased | 10009775 |
| International normalised ratio abnormal | 10022592 |
| International normalised ratio increased | 10022595 |
| Protein C decreased | 10037005 |
| Protein S abnormal | 10051736 |
| Protein S decreased | 10051120 |
| Prothrombin level abnormal | 10037048 |
| Prothrombin level decreased | 10037050 |
| Prothrombin time abnormal | 10037057 |
| Prothrombin time prolonged | 10037063 |
| Prothrombin time ratio abnormal | 10061918 |
| Prothrombin time ratio increased | 10037068 |
| Thrombin time abnormal | 10051319 |
| Thrombin time prolonged | 10051390 |

## 8.3 Appendix 3: GRACE risk score

The GRACE risk score at the presentation of the index event will be calculated as follows:

```
* 1.  Killip class I,II,III,IV;
     if killip=1 then killips = 0;
else if killip=2 then killips = 20;
else if killip=3 then killips = 39;
else if killip=4 then killips = 59;

* 2.  BPSYS is systolic blood pressure (mm Hg);

     if  0 <=bpsys <  80 then sysbp2 = 58;
else if 80 <=bpsys < 100 then sysbp2 = 58 -(bpsys-80)*(10/20);
else if 100<=bpsys < 110 then sysbp2 = 48 -(bpsys-100)*(5/10);
else if 110<=bpsys < 120 then sysbp2 = 43 -(bpsys-110)*(4/10);
else if 120<=bpsys < 130 then sysbp2 = 39 -(bpsys-120)*(5/10);
else if 130<=bpsys < 140 then sysbp2 = 34 -(bpsys-130)*(5/10);
else if 140<=bpsys < 150 then sysbp2 = 29 -(bpsys-140)*(5/10);
else if 150<=bpsys < 160 then sysbp2 = 24 -(bpsys-150)*(5/10);
else if 160<=bpsys < 180 then sysbp2 = 19 -(bpsys-160)*(9/20);
else if 180<=bpsys < 200 then sysbp2 = 10 -(bpsys-180)*(10/20);
else if      bpsys >=200 then sysbp2 = 0;

* 3.  PULSE in beats/minute;

     if  0 <=pulse < 50 then pulse2 = 0;
else if 50 <=pulse < 60 then pulse2 = 0  + (pulse-50)*(3/10);
else if 60 <=pulse < 70 then pulse2 = 3  + (pulse-60)*(3/10);
else if 70 <=pulse < 80 then pulse2 = 6  + (pulse-70)*(3/10);
else if 80 <=pulse < 90 then pulse2 = 9  + (pulse-80)*(3/10);
else if 90 <=pulse < 100 then pulse2 = 12 + (pulse-90)*(3/10);
else if 100<=pulse < 110 then pulse2 = 15 + (pulse-100)*(3/10);
else if 110<=pulse < 150 then pulse2 = 18 + (pulse-110)*(12/40);
else if 150<=pulse < 200 then pulse2 = 30 + (pulse-150)*(16/50);
else if      pulse >=200 then pulse2 = 46;

* 4.  AGE in years;

     if  0 <=age < 30 then age2 = 0;
else if 30 <=age < 40 then age2 = 0  + (age-30)*(17/10);
else if 40 <=age < 50 then age2 = 17 + (age-40)*(16/10);
else if 50 <=age < 60 then age2 = 33 + (age-50)*(17/10);
else if 60 <=age < 70 then age2 = 50 + (age-60)*(17/10);
else if 70 <=age < 80 then age2 = 67 + (age-70)*(16/10);
else if 80 <=age < 90 then age2 = 83 + (age-80)*(17/10);
else if      age >=90 then age2 = 100;
```

```
* 5.  Creatinine in mg/dl;
(If creatinine is in micromole / L, then
Creatinine in mg/dL = (Creatinine in micromole/L) / 88.4

     if 0.0 <=creat_mg < 0.2 then crt2 = 0  + (creat_mg-0)*(1/.2);
else if 0.2 <=creat_mg < 0.4 then crt2 = 1  + (creat_mg-0.2)*(2/.2);
else if 0.4 <=creat_mg < 0.6 then crt2 = 3  + (creat_mg-0.4)*(1/.2);
else if 0.6 <=creat_mg < 0.8 then crt2 = 4  + (creat_mg-0.6)*(2/.2);
else if 0.8 <=creat_mg < 1.0 then crt2 = 6  + (creat_mg-0.8)*(1/.2);
else if 1.0 <=creat_mg < 1.2 then crt2 = 7  + (creat_mg-1.0)*(1/.2);
else if 1.2 <=creat_mg < 1.4 then crt2 = 8  + (creat_mg-1.2)*(2/.2);
else if 1.4 <=creat_mg < 1.6 then crt2 = 10 + (creat_mg-1.4)*(1/.2);
else if 1.6 <=creat_mg < 1.8 then crt2 = 11 + (creat_mg-1.6)*(2/.2);
else if 1.8 <=creat_mg < 2.0 then crt2 = 13 + (creat_mg-1.8)*(1/.2);
else if 2.0 <=creat_mg < 3.0 then crt2 = 14 + (creat_mg-2.0)*(7/1);
else if 3.0 <=creat_mg < 4.0 then crt2 = 21 + (creat_mg-3.0)*(7/1);
else if       creat_mg >=4.0 then crt2 = 28;

* 6.  STCHANGE is ST deviation, assigned a value of 1 if present, 0 if
absent;

* 7.  POSINIT is positive initial cardiac enzymes (1 if present, 0 if
absent);

* 8.  CARRST is cardiac arrest on presentation (1 if present, 0 if absent);

* Risk score=sum of points for 8 factors;

Death_pt = killips + sysbp2 + pulse2 + age2 + crt2 + 28*stchange

+ 14*posinit + 39*carrst;
```

The GRACE risk score at the discharge will be calculated as follows:

```
* 1.  Age in years;
     if  0 <=age < 35 then age_sc = 0;
else if 35 <=age < 45 then age_sc = 0  + (age-35)*((18-0)/10);
else if 45 <=age < 55 then age_sc = 18 + (age-45)*((36-18)/10);
else if 55 <=age < 65 then age_sc = 36 + (age-55)*((55-36)/10);
else if 65 <=age < 75 then age_sc = 55 + (age-65)*((73-55)/10);
else if 75 <=age < 85 then age_sc = 73 + (age-75)*((91-73)/10);
else if 85 <=age < 90 then age_sc = 91 + (age-85)*((100-91)/5);
else if      age >=90 then age_sc = 100;

* 2.  Pulse at presentation, in beats/minute;

     if  0 <= pulse < 50 then pulse_sc = 0;
else if 50 <= pulse < 60 then pulse_sc= 0 + (pulse-50)*((3-0)/10);
else if 60 <= pulse < 80 then pulse_sc= 3 + (pulse-60)*((9-3)/20);
else if 80 <= pulse < 100 then pulse_sc= 9 + (pulse-80)*((14-9)/20);
else if 100 <= pulse < 130 then pulse_sc= 14 + (pulse-100)*((23-14)/30);
else if 130 <= pulse < 175 then pulse_sc= 23 + (pulse-130)*((35-23)/45);
else if 175 <= pulse < 200 then pulse_sc= 35 + (pulse-175)*((43-35)/25);
else if        pulse >=200 then pulse_sc= 43;
```

```
* 3.  Systolic blood pressure at presentation, in mm Hg;

     if  0 <=bpsys< 80 then sbp_sc =   24;
else if 80 <=bpsys< 90 then sbp_sc =   24 - (bpsys-80)*((24-22)/10);
else if 90 <=bpsys< 110 then sbp_sc =  22 - (bpsys-90)*((22-18)/20);
else if 110 <=bpsys< 130 then sbp_sc = 18 - (bpsys-110)*((18-14)/20);
else if 130 <=bpsys< 150 then sbp_sc = 14 - (bpsys-130)*((14-10)/20);
else if 150 <=bpsys< 180 then sbp_sc = 10 - (bpsys-150)*((10-4)/30);
else if 180 <=bpsys< 200 then sbp_sc =  4 - (bpsys-180)*((4-0)/20);
else if       bpsys>=200 then sbp_sc =  0;

* 4.  Initial creatinine in mg/dL;
(If creatinine is in micromole / L, then
Creatinine in mg/dL = (Creatinine in micromole/L) / 88.4

     if   0 <= creat < 0.2 then creat_sc = 0 + (creat-0.0)*((1-0)/0.2);
else if 0.2 <= creat < 0.4 then creat_sc = 1 + (creat-0.2)*((2-1)/0.2);
else if 0.4 <= creat < 0.6 then creat_sc = 2 + (creat-0.4)*((3-2)/0.2);
else if 0.6 <= creat < 0.8 then creat_sc = 3 + (creat-0.6)*((4-3)/0.2);
else if 0.8 <= creat < 1.0 then creat_sc = 4 + (creat-0.8)*((5-4)/0.2);
else if 1.0 <= creat < 1.2 then creat_sc = 5 + (creat-1.0)*((6-5)/0.2);
else if 1.2 <= creat < 1.4 then creat_sc = 6 + (creat-1.2)*((7-6)/0.2);
else if 1.4 <= creat < 1.6 then creat_sc = 7 + (creat-1.4)*((8-7)/0.2);
else if 1.6 <= creat < 1.8 then creat_sc = 8 + (creat-1.6)*((9-8)/0.2);
else if 1.8 <= creat < 2.0 then creat_sc = 9 + (creat-1.8)*((10-9)/0.2);
else if 2.0 <= creat < 3.0 then creat_sc = 10+ (creat-2.0)*((15-10)/1.0);
else if 3.0 <= creat < 4.0 then creat_sc = 15+ (creat-3.0)*((20-15)/1.0);
else if       creat >=4.0 then creat_sc = 20;

* for 5-8, code 0 if absent, 1 if present;

* 5.  POSINIT is initial elevated serum cardiac biomarkers;

* 6.  STDEPR is ST-segment depression on initial ECG;

* 7.  MHMI   is history of MI (as of hospital admission);

* 8.  MHCHF  is history of CHF (as of hospital admission);

* 9.  NOPCI    is PCI performed in hospital (code 1=no PCI, 0=PCI);

* Risk score=sum of points for 9 factors;

*** equation;
escore = age_sc + pulse_sc + sbp_sc + creat_sc + 15*posinit
       + 11*stdepr + 12*mhmi + 24*mhchf + 14*nopci;
```