Protocol for Phase II Study of YM150

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 Subjects with Acute Coronary Syndromes.

The RUBY-1 study

Sponsor: Astellas Pharma Europe B.V. (APEB)

Address: PO Box 108, 2350 AC Leiderdorp, The Netherlands

ISN/Protocol: 150-CL-201

EudraCT number: 2008-005972-29

Original Protocol final version 14 May 2009, including Amendment 01, version 2.0, 03 March 2010

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

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 Subjects with Acute Coronary Syndromes. The RUBY-1 study

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2. COORDINATING INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the sponsor.
I agree that it contains all the information required to conduct this study.
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Signature: _____ 05 /Mar/2010
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3. INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

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III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
aPTT	Activated Partial Thromboplastin Time
ASA	Acetyl Salicylic Acid
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration – time curve
b.i.d.	Twice daily administration
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Competitive Authorities
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C.I.R.T.	Cenduit Interactive Response Technology
C_{max}	Maximum concentration
CK-MB	Creatine Kinase Myocardial Band
CRF	Case Report Form
CRNM	Clinically Relevant Non Major
CRO	Contract Research Organization
CT	Computed Tomography
CUA	Cost-Utility Analysis
CV	Curriculum Vitae
^{14}C-YM150	YM150 labeled with a carbon-14 radioactive isotope
DDI	Drug-drug interaction
DM2	Diabetes mellitus type 2
DSMB	Data and Safety Monitoring Board
DSP	Drug Safety and Pharmacovigilance
DVT	Deep Vein Thrombosis
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
GMP	Good Manufacturing Practice
GGT	Gamma-Glutamyl Transferase
GP	Glycoprotein
HR	Hazard Ratio

HRQoL	Health-Related Quality of Life
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
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
LFT	Liver Function Test
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NOAEL	No Observed Adverse Effect level
NSAIDS	Non Steroidal Anti Inflammatory Drugs
NSTE	Non ST Elevation
NYHA	New York Heart Association
NVAF	Non Valvular Atrial Fibrillation
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PT	Prothrombin Time
PTM	Placebo to match tablets
QALY	Quality Adjusted Life Years
q.d.	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
SC	Steering Committee
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
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{½}$	Apparent Terminal Elimination Half-life
t_{max}	Time to Attain C_{max}
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction

TPA	Tissue Plasminogen Activator
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

List of Key Study Terms

Terms	Definition of terms
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the present study. 2) Time when 'Baseline' is observed.
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject 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. Informed consent precedes enrollment, which precedes or is contemporaneous with randomization.
Index Event	Subject presents with NSTE-ACS or STE-ACS at the hospital for which he 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 subject, 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 subject enrolling into study until just before the test drug or comparative drug (sometimes without randomization) is given to a subject .
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 subject to the treatment group or treatment cohort. Depending on the type of rules for handling for study drugs, 'Randomization' is usually executed just before entering the 'investigational period'.
Screening	1) Process for retrieving candidates for the study. 2) Process for checking the eligibility of subjects usually done during the "pre-investigational period".
Screening failure	Screened subject, 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.
Subject	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.

IV. SYNOPSIS

Title of Study	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 Subjects with Acute Coronary Syndromes. The RUBY-1 study
Planned Study Period	September 2009 – December 2010 (nine months recruitment, six months double-blind treatment period, four weeks follow up period)
Study Objectives	Primary Objective: • To evaluate the safety and tolerability of different doses and dose regimens of YM150 on top of standard treatment with Acetyl Salicylic Acid (ASA) with or without clopidogrel in the secondary prevention of Ischemic Vascular Events in Subjects with recent ACS. Secondary Objectives: • To evaluate the efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA with or without clopidogrel in the secondary prevention of Ischemic Vascular Events in Subjects with recent ACS, • To compare safety, tolerability and efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA with or without clopidogrel against placebo. Other Objectives: • To assess Pharmacokinetic and Pharmacodynamic (PKPD) properties in the target population, • To further define the suitable subject population for further development (i.e. P III).
Planned Total Number of Study Centers and Location	Approximately 200 centers in Europe, Latin America, South East Asia, etc.
Design and Methodology:	A prospective, randomized, double-blind, multi-center, multiple dose, placebo controlled, parallel group study. Six dose groups of YM150 and one placebo control group will be evaluated in a double-blind fashion. After subjects have presented with the index event they will be screened for eligibility. If considered eligible subjects will be randomized in a double-blind fashion to one of the seven study treatment groups as early as possible after clinical stabilization, but after discontinuation of parenteral antithrombotics, but within 7 days after presentation with the index event. The double-blind study drug will be given in addition to standard antiplatelet treatment as described below.

	During the double-blind study period all subjects will receive antiplatelet treatment per standard of care according to (local) guidelines: ● 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. The study organization will consist of a Steering Committee (SC), an Independent Adjudication Committee (IAC) and an independent Data and Safety Monitoring Board (DSMB). The SC has contributed to the study design and protocol development and has shared scientific responsibility on the protocol. Moreover the SC will advise Astellas following recommendations of the DSMB. A blinded IAC will adjudicate the specified study outcomes centrally. An independent DSMB will periodically review unblinded data and give recommendations to the SC and Astellas regarding the continuation or termination of a dose group of YM150 or the overall study. The responsibilities and deliverables of the above mentioned committees and board will be described in respective charters.
Number of Subjects Planned:	158 subjects will be randomized to each YM150 dose group and 316 subjects to the placebo group, for a total of 1264 subjects randomized. Assuming the incidence of Major and Clinically Relevant Non Major (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.
Main Selection Criteria:	Subjects have to meet all inclusion criteria and none of the exclusion criteria in order to be eligible for randomization. **Inclusion criteria** are: male or female subject who: 1. has a diagnosis of STE-ACS, NSTE-ACS as index event according to accepted guidelines such as the ESC or AHA guideline, 2. has elevated cardiac biomarkers (cardiac Troponin T or I or CK-MB) >2x ULN for CK-MB or > ULN for troponin, 3. either has STE-ACS, or for subjects with a diagnosis of NSTE-ACS, at least one of the following additional high risk

	factors for ischemic events must be present: • ST deviations on Electrocardiogram (ECG) at any time between presentation of the index event and randomization • Age of 65 years or older • Previous ACS < 12 months prior to randomization • Multi vessel Coronary Artery Disease (CAD) • Ischemic stroke or Transient Ischemic Attack (TIA) > 12 months prior to randomization • Type 2 Diabetes Mellitus • Peripheral Arterial Disease (PAD) 4. is clinically stable which is defined as discontinuation of parenteral antithrombotics and is not likely to require reinstallment of parenteral antithrombotics at time of randomization and receives current standard oral antiplatelet therapy, 5. is able to be randomized within 7 days after presentation with STE-ACS or NSTE-ACS following management to current best clinical practice in the study centre. This may include thrombolysis or primary Percutaneous Coronary intervention (PCI) for STE-ACS, or early invasive strategy (including PCI) for non-STE-ACS subjects. Subjects should be randomized as soon as possible after discontinuation of parenteral antithrombotics, 6. has provided Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations or Informed Consent has been obtained from the legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable), 7. is 18 years of age (legal minimum age required per country) or older at time of informed consent. **Exclusion criteria** at time of randomization: subject 1. requires ongoing parenteral or oral anticoagulant therapy (such as vitamin K antagonists, Unfractionated Heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, thrombin inhibitors), thrombolytics (such as Tissue Plasminogen Activator (TPA), streptokinase), Glycoprotein (GP) IIb/IIIa antagonists or other antiplatelet drugs (such as cilostazol, ticlopidine, dipyridamole, prasugrel), 2. is planned for myocardial revascularization (e.g., Coronary Artery Bypass Graft (CABG) or elective or staged PCI) or any other invasive procedure with increased risk for bleeding (i.e. elective surgical procedures) within 60 days after

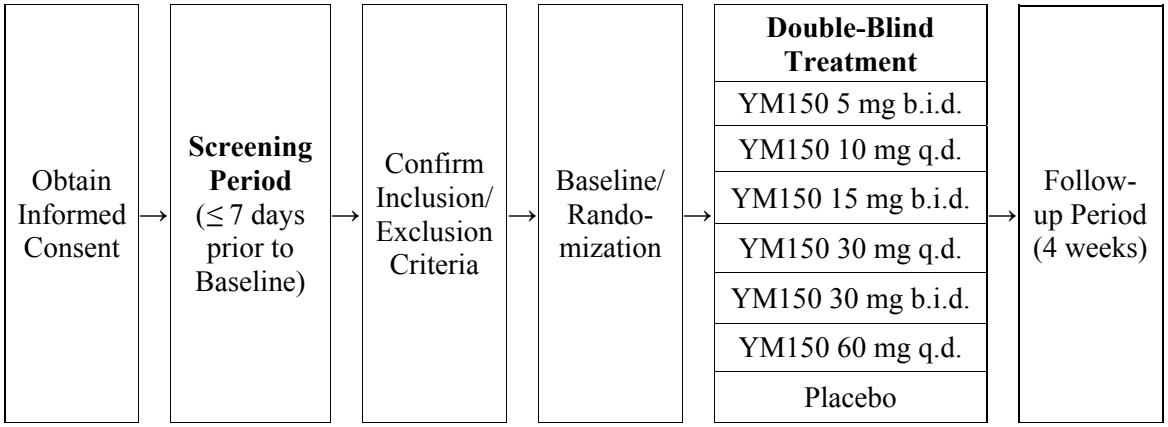
	randomization, 3. has active bleeding or is in the opinion of the investigator at high risk of bleeding during the study, 4. has had recent stroke or TIA ≤ 12 months prior to index event, 5. has a bleeding diathesis or any other condition or laboratory abnormality with an increased tendency for bleeding (e.g., platelet count below 100.000/uL), 6. is a female of childbearing potential who refuses to use a medically acceptable form of contraception throughout the study. Acceptable methods of contraception include the following: oral or injectable hormonal contraceptives, intrauterine devices, vaginal hormonal rings, and only in combination with a male condom, a vaginal diaphragm or cervical caps. Male study subjects should be advised to use male condom in addition to having their partner use another acceptable method during the study and for three months after the last dose, 7. is a female who is pregnant or lactating or has a positive pregnancy test within 72 hours prior to randomization; 8. has persistent blood pressure of 160 mmHg systolic or higher and/or 100 mmHg diastolic or higher at baseline with or without medication, 9. has hepatic insufficiency or presents with ALT > 2.0 times the ULN or total bilirubin > 1.5 times the ULN (result based on (local) laboratory testing on blood sample drawn within maximally 24 hours prior to randomization), 10. has a estimated renal creatinine clearance of <60 mL/min as calculated by the Cockcroft-Gault equation (result based on (local) laboratory testing on blood sample drawn maximally 24 hours prior to randomization), 11. has any concurrent illness which, in the opinion of the investigator, may interfere with treatment or evaluation of safety or completion of this study, 12. has participated in another clinical trial of an investigational drug (including placebo) or device within 30 days (or the limit set by national law, whichever is longer) of signing informed consent for the present study, 13. has participated in any YM150 clinical trials, 14. has known allergy to the study drug or any of its components.
Discontinuation Criteria (Optional):	See section 3.4 Discontinuation Criteria for Individual Subjects.
Test Drug Dose: Mode of	All subjects will receive three tablets of YM150 and/or placebo to match tablets (PTM) per day in a double-blind fashion to guarantee adequate blinding of the once daily and the twice daily

Administration: **Duration of Treatment:**	groups: ● Group 1: YM150 5 mg b.i.d., ● Group 2: YM150 10 mg q.d., ● Group 3: YM150 15 mg b.i.d., ● Group 4: YM150 30 mg q.d., ● Group 5: YM150 30 mg b.i.d., ● Group 6: YM150 60 mg q.d., ● Group 7: Placebo. The allocation ratio will be 1:1:1:1:1:1: 2. Randomization will be stratified by country and clopidogrel use. Tablets are to be taken orally with adequate fluids. Subject will receive double-blind treatment with YM150 or placebo for a total duration of 26 weeks.
Reference Therapy Dose: **Mode of Administration:** **Duration of Treatment:**	Placebo will be given as reference in the placebo dose group, Group 7. For this purpose and for the placebo tablets to guarantee adequate blinding of the once daily and the twice daily groups two types of placebo to match tablets are available. One to match the 5, 10, 15 and 30 mg tablets and one to match the 60 mg tablets. All subjects will take twice daily study drug.
Concomitant Medication	The number of hours that the following antithrombotics needs to be discontinued prior to intake of the first dose of double-blind study drug is: • Parenteral UFH needs to be stopped at least 2 hours, • Bivalirudin needs to be stopped at least 2 hours, • LMWH need to be stopped at least 8 hours, • Fondaparinux needs to be stopped at least 18 hours, • GP IIb/IIIa antagonists need to be stopped o at least 12 hours for abciximab o at least 6 hours for eptifibatide or tirofiban. Concomitant use of anticoagulants (such as 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. 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. For further details please see section 5.1.3.
Primary Variables	Major and CRNM bleeding events (ISTH definition) at six months
Statistical Methods	The Safety Analysis Set (SAF) and the Full analysis set (FAS) will include all randomized subjects who received at least one dose of study drug (active or placebo). The Per Protocol Set

	(PPS) will include all evaluable FAS subjects who do not have any major protocol violations. All variables will be summarized by descriptive statistics for each randomization arm and grouped by treatment (placebo/YM150), YM150 regimen (once daily/twice daily) and daily dose (10mg/30mg/60mg). The cumulative risk both at day 30 and at month 6 will be provided for all primary and selected secondary variables and for each randomization arm (and grouped by treatment, regimen and daily dose) using Kaplan-Meier estimates. The estimated cumulative risk function versus time using Kaplan-Meier estimates will be plotted for each randomization arm (and grouping by treatment, regimen and daily dose). Primary analysis will be provided for the Full Analysis Set (FAS) and stratified for standard antiplatelet treatment (ASA or ASA + clopidogrel). Subjects using only clopidogrel will be included in the ASA+clopidogrel group. The primary safety variable, incidence of Major and CRNM bleeding events (ISTH definition) at six months, will be inferentially analyzed using a Cox regression model including YM150 regimen (q.d. or b.i.d.) and the total daily dose adjusted for standard antiplatelet treatment (ASA or ASA + clopidogrel). The hazard ratio (HR) and its 95% confidence interval (CI) will be presented for: ● YM150 dose trend (represents the expected increase of risk when YM150 dose is doubled).

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Start and End of Study

The start of the study is defined as the date of first subject's signed informed consent and the end of the study is defined as the last subject's last protocol-defined assessment.

Schedule of Assessments

The schedule of assessments is included in Table 1.

Table 1: Schedule of Assessments

	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 medication		
Informed Consent/Authorization [f]	X									
Verify Inclusion/Exclusion Criteria	X	X								
Medical History	X	X [g]								
Height		X								
Weight		X						X		
Vital Signs (BP 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	

	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 medication		
Adverse Events [u]		X	X	X	X	X	X	X	X	X [v]
Vital Status										X

[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 (subjects should have first dose of YM150 study drug administered at the physician's office).

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

[e] For subjects 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 subject. This can be performed by a telephone consult (TC) with the subject.

[f] Subject 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, BUN, Creatinine, ALP, AST, ALT, GGT, 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, RBC, 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 CK-MB levels based on local laboratory results.

[k] ALT, estimated creatinine clearance (according to Cockcroft-Gault Equation (see Appendix 4), 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 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 m and n below).This PK/PD sampling in the

morning at V5 can be switched to V7 if more practical for the subject. 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 visit 5 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 subject with the morning PK/PD sample then being taken at V7.

[n] Blood sampling for PK/PD assessment for visit V5 (Week 6) should be scheduled in the morning before 13:00: subject 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 visit 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 subjects for self intake at home

[s] Subjects 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 subject 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 subject 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.

1 INTRODUCTION

1.1 Background

Background on target indication
Epidemiology of cardiovascular disease

Cardiovascular disease remains the leading cause of death worldwide (Murray, 1997), causing nearly one-third of all deaths in women and over one-quarter in men in 2004 (WHO report 2004). In the same year, coronary heart disease was responsible for one in every five deaths in the US, and was the most frequent cause of death in US adults (American Heart Association, 2008).

Acute coronary syndromes

Acute coronary syndromes (ACS) represent a critical phase in the evolution of coronary artery disease (CAD). Patients with an ACS encompass a heterogeneous group of individuals with varying clinical presentation and extent of underlying coronary disease (Steg, 2002). However, these conditions share a common underlying pathophysiology, specifically rupture or erosion of coronary artery atherosclerotic plaque, responsible for thrombus formation leading to varying degrees of coronary obstruction and embolization causing myocardial ischemia and necrosis (Falk, 1995; Hamm, 2006). Based on electrocardiographic data and cardiac biomarkers, ACS subjects can be categorized in ST- or non-ST-segment elevation ACS at presentation. At the time of discharge, these subjects will evolve towards Q-wave Myocardial Infarction (MI), non-Q-wave MI, or unstable angina.

Secondary prevention of ACS

The management of ACS has evolved considerably over the past three decades with improvements in therapeutic options, leading to a dramatic decline in morbidity and mortality in recent years (Fox, 2007).

Guidelines from the European Society of Cardiology (ESC) (Van de Werf, 2008; Bassand, 2007) and the American College of Cardiology/American Heart Association (ACC/AHA) (Anderson, 2007; Antman, 2004), which are derived largely from data from large-scale randomized controlled trials (Yusuf, 2001; Mehta, 2001; Steinhubl, 2002), recommend the continuation of dual antiplatelet therapy (Acetylsalicylic acid (ASA) and clopidogrel) for up to 1 year after an ACS.

Despite this potent dual antiplatelet therapy, the recurrence of ischemic events after an ACS remains high, up to 9.1% at six months (Fox, 2006), generating interest for further or more potent antithrombotic therapy in addition to the current standard of antiplatelet therapy. Since thrombin plays a pivotal role in the formation and consolidation of thrombus in ACS, there has been interest in thrombin inhibitors, particularly as oral forms have recently become available. Conventional oral anticoagulation with vitamin K antagonists is fraught with problems related to the narrow therapeutic margin of these agents, the need for careful monitoring, the frequent interactions with drugs and food, and the delay in onset and offset of action. In addition, and largely because of the above, there are strong data to show that

chronic triple antithrombotic therapy with ASA, thienopyridines, and vitamin K antagonists beyond the acute phase is associated with a high bleeding risk (Karjalainen, 2007). In this context, more selective oral anticoagulants such as Factor Xa (FXa) inhibitors and direct thrombin inhibitors have raised interest.

New anticoagulant therapies in ACS
Oral direct thrombin inhibitors

The first direct thrombin inhibitor to be approved for oral use was ximelagatran. The Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM) trial (Wallentin, 2003) compared ximelagatran to placebo in combination with ASA alone after a recent ACS and found a significant reduction in ischemic events associated with a doubling in bleeding events. These results highlight the potential for benefit with oral anticoagulation in addition to antiplatelet therapy after ACS. However, they cannot be extrapolated to current clinical practice as subjects undergoing PCI were excluded from the study and subjects did not receive dual antiplatelet therapy. Moreover, ximelagatran was withdrawn from the market in 2006 following concerns over hepatotoxicity.

The Phase II RE-DEEM trial of another oral direct-thrombin inhibitor, dabigatran, is currently recruiting subjects. In this trial, four doses of dabigatran are being evaluated. Dabigatran is given on top of ASA and clopidogrel. Patients undergoing PCI are not excluded from the study, reflecting the contemporary environment of ACS care.

Factor Xa inhibitors

The synthetic pentasaccharide fondaparinux is an indirect synthetic FXa inhibitor. In the Organization to Assess Strategies for Ischemic Syndromes-6 (OASIS-6), study involving subjects with acute ST-elevation MI, fondaparinux was superior to Unfractionated Heparin (UFH) in preventing death or reinfarction in subjects not undergoing PCI (Yusuf, 2006). In a combined analysis of all ACS subjects in OASIS-5 and OASIS-6, compared with a heparin-based (dose-adjusted UFH or enoxaparin) strategy, fondaparinux reduced risk of death, ischemic events, and major bleeding, and was associated with a better combined clinical outcome in individuals undergoing invasive or conservative management (Mehta, 2008). While this therapy is effective, concerns remain over risk of bleeding (Bassand, 2007), and it also has the disadvantage of an intravenous route of administration, which limits its utilization beyond the acute phase.

New oral FXa inhibitors under investigation include rivaroxaban (BAY 59-7939) (Haas, 2009; Kakar, 2007(A); Kakar, 2007(B); Perzborn, 2007; Piccini, 2008), YM150 (Eriksson, 2007), DU-176b (Hylek, 2007), and apixaban (BMS-562247) (Buller, 2008; Lassen 2007).

The Phase II APPRAISE-I study (Alexander, 2008) evaluated apixaban on top of ASA and clopidogrel. The results from this trial were presented at the ESC congress in Munich in 2008. The authors reported a non-statistically significant trend towards a lower rate of ischemic events associated with a higher bleeding event rate in subjects receiving apixaban, especially in those on the higher dose.

ATLAS ACS TIMI 46 (Rivaroxaban in Combination With ASA Alone or With ASA and a Thienopyridine in Subjects With Acute Coronary Events) is a Phase II study evaluating rivaroxaban in subjects with an ACS. The data for this study were presented at the AHA scientific sessions in November 2008. The primary endpoint, combining all-cause death, MI, stroke, or severe ischemia requiring revascularization, did not reach statistical significance and resulted in a dose-dependent increase in bleeding. ATLAS 2 TIMI 51 will be a Phase II study randomizing subjects between placebo and two doses of rivaroxaban on top of aspirin and a thienopyridine.

YM150 pharmacology and development strategy

FXa is a pivotal blood coagulation factor common to both the extrinsic and the intrinsic coagulation cascades. Therefore, FXa inhibitors are anticipated to be an effective anticoagulant therapy for prevention and possible treatment of thrombosis and thromboembolic events. Results of clinical trials with the pentasaccharide fondaparinux, a selective FXa inhibitor, support this concept [Bauer et al, 2002].

YM150 and its major metabolite YM-222714 are direct inhibitors of FXa. Since direct FXa inhibitors are small molecules that bind to and inhibit FXa independent of other proteins, they are thought to bind with clot-bound FXa as well as free FXa.

The potential effect of YM150, a direct FXa inhibitor, on Venous Thromboembolism (VTE) prophylaxis was shown in two Phase II studies (studies 150-CL-003 and 150-CL-008). In both studies, the incidence of VTE decreased markedly with increasing daily doses of YM150 supporting the antithrombotic concept of direct oral FXa inhibition in this subject population. The efficacy and safety of YM150 in prophylaxis of VTE in subjects undergoing orthopaedic surgery is further evaluated in several Phase IIb and III studies.

Based on the above, YM150 will be evaluated in prevention of stroke in subjects with Non Valvular Atrial Fibrillation (NVAF) in a Phase II study (150-CL-021).

In current RUBY-1 study (150-CL-201) the safety, tolerability and efficacy of YM150 in secondary prevention of ischemic vascular events in subjects with recent ACS will be investigated.

The primary objective of this prospective, randomized, double-blind, multi-center multidose, placebo controlled, parallel group study is to evaluate the safety and tolerability of different doses and dose regimens of YM150 on top of standard treatment with ASA, with or without clopidogrel, in the secondary prevention of ischemic vascular events in subjects with a recent ACS (ST elevation or non-ST elevation ACS). The secondary objectives are to evaluate the efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA, with or without clopidogrel, in the secondary prevention of ischemic cardiovascular events; to compare the safety, tolerability, and efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA, with or without clopidogrel, versus placebo; to assess the PKPD properties in the target population; and to further define the suitable subject population for development in Phase III studies.

1.2 Non-clinical and Clinical Data

Non-clinical and clinical information is summarized in this section.

For detailed information about the non-clinical and clinical studies performed with YM150, see the latest version of the YM150 Investigator's Brochure (IB).

1.2.1 Pharmacodynamic Properties

YM150 and YM-222714, the active glucuronide metabolite of YM150 presumed to be responsible for the in vivo activity, were equipotent in vitro when tested in models for Factor Xa (FXa) inhibition and prolongation of blood coagulation. During the in vivo studies in rodents, the antithrombotic properties of YM150 were compared with those of fondaparinux, ximelagatran, enoxaparin, warfarin and rivaroxaban. The results suggest that selective FXa inhibitors such as YM150, in contrast to thrombin inhibitors, may exert antithrombotic effects at doses with little or no effect on blood coagulation and bleeding times. Furthermore, when combined with clopidogrel or aspirin, YM150 augmented the antithrombotic effect of each antiplatelet without prolonging the bleeding time.

Five non-clinical pharmacology reports have been finalized recently, the summary of the results are presented below. Please refer to the current version of the IB for further information.

These studies showed that YM150 and rivaroxaban both have an antithrombotic effect in the mice model of $FeCl_3$-induced arterial thrombosis (150-PH-047/048). The PT clotting assay, including the INR conversion, is not appropriate for anticipating the PD effects of direct FXa inhibitors unless the assay method can be standardized (150-PH-049). Tissue factor concentration does not affect the anticoagulant properties of YM150 and YM-222714, which is in contrast to rivaroxaban and apixaban (150-PH-050). YM150 and YM-222714 show no effects on major serine proteases, including the fibrinolysis system and blood coagulation cascade, indicating that they are selective inhibitors of FXa (150-PH-051). The recently identified metabolite AS2486616-NA was shown to be pharmacological active, although the potency is less than 1/30 of those for YM-222714 (150-PH-052).

1.2.2 Pharmacokinetic Properties

After single and multiple oral administrations to rats and dogs, YM150 was extensively converted upon first passage of the intestine and/or liver into YM-222714 (glucuronide of YM150). YM-221951 (sulphate of YM150), YM-228934 (N-desmethylate of YM150) and AS2486616 (N-oxide of YM-222714) concentrations in plasma were substantially lower than YM-222714 concentration. In vitro plasma protein binding of YM150 in different species (including humans) was comparable and moderate (80.9-85.5%). In contrast, YM-222714 in vitro plasma-protein binding differed between species, but was 73.9-77.0% in humans. Results from in vitro microsomal studies conducted with YM150 and YM-222714 do not predict drug-drug interactions (DDI) with concomitant medications metabolized by human cytochrome-P450 (CYP) isoenzymes. In vitro studies in Caco-2 cells showed that YM150 and YM-222714 are weak inhibitors of Pgp. A drug-drug interaction between YM150 or YM-222714 with a concomitant Pgp substrate is not expected. YM150 and YM-222714 have

no inhibitory effect on hMRP2-mediated transport.
Placental transfer of radioactivity to fetuses was low after oral administration of ^{14}C-YM150 to pregnant rats and radioactivity was found to transfer to breast milk of lactating dams.

Human pharmacology studies have shown that the parent compound, YM150, was detected at low levels, since YM150 is rapidly absorbed and extensively metabolized into YM-222714, the main and active metabolite. The mean C_{max} and AUC of YM-222714 appeared to increase dose-proportionally across the tested dose range. First and last dose AUC values were comparable, indicative of time-independent pharmacokinetics (PK). The maximum plasma (C_{max}) concentration is reached within 1 to 2 hours (t_{max}). The mean elimination half-life ($t_{1/2}$) of YM-222714 ranged from 14 to 20 hours, and appeared to be independent of the dose.

Steady state plasma levels were reached within 5 days. A population PK meta-analysis has been performed including Phase I and II studies. The results of this analysis showed only limited effects of age and sex on the pharmacokinetics of YM-222714. For example, in Study 150-CL-008 the mean AUC of YM-222714 at 60 mg YM150 amounted to 13906 ng·h/mL in male and 15044 ng·h/mL in female subjects undergoing total hip arthroplasty. Minimal differences in PK between Caucasian and Japanese subjects were observed. The most relevant covariate for the PK of YM-222714 appeared to be creatinine clearance; with decreasing creatinine clearance, AUC increases. The PK of YM-222714 was minimally affected when study drug was taken with food.

The main metabolic pathway is glucuronidation while YM150 and its metabolites are excreted by the kidneys and intestines mainly as the main metabolite YM-222714.

No interaction was observed when YM150 was co-administered with digoxin in healthy subjects (Study 150-CL-007).

1.2.2.1 Toxicokinetics of chronic toxicity studies

YM150 and YM-222714 exposure (C_{max} and AUC_{0-24}) from the 52-week high dose repeated-dose toxicity study in dogs are presented in Table 2. The observed toxicokinetics are consistent with previous observations (see current version of the IB).

Table 2: Summary of exposure in 52-week high dose dog toxicology study of YM150

Study	Time	Dose (mg/kg)	YM150				YM-222714				HED (mg/kg)
			C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)		C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)		
			M	F	M	F	M	F	M	F	
52-Week Dog Oral gavage n=4-7[1]	Day 1	60	43.1	55.6	170	257	2294	3993	9091	15932	32.4
		100	58.3	100	421	414	3502	4255	18206	22803	54
	Week 26	60	56.3	53.8	381	269	5034	3228	32055	16217	32.4
		100	71.2	54.7	314	298	3271	1819	19990	9066	54
	Week 52	60	56.3	74.9	203	308	2374	3133	8879	14389	32.4
		100	43.6	175	305	640	2411	4022	16384	15050	54

Source: Study 150-TX-030 (dog)
[1] 3 animals were necropsied at 26 weeks. M: male; F: female; HED: Human equivalent dose: equivalence was based on human weight of 60 kg after taking into account the species differences in body surface area. Since the 52-week high dose repeated -dose study was an extension of the 52-week repeated-dose toxicity study 150-TX-016 no NOAEL was estimated.

1.2.3 Non-Clinical Safety Data

Non-clinical safety pharmacology and toxicology studies that have been conducted include repeated-dose studies in rats, dogs and monkeys up to 26, 52 and 2 weeks, respectively, fertility and pre- and postnatal development toxicity studies in rats, embryo-fetal toxicity studies in rats and rabbits, skin sensitization study in guinea pigs, genotoxicity studies, in vitro phototoxicity studies and core safety pharmacology studies. Both safety pharmacology and toxicology studies in rats, dogs and monkeys demonstrated effects that can be primarily attributed to the pharmacological action of YM150. The low incidence of bleeding in animals even at very high doses underlines the safety of the compound. In rats, toxicity was limited to the formation of crystals in urine and related damage to the kidney. In dogs, treatment with YM150 caused basophilia and slight necrosis in the proximal tubular epithelium. The liver is the second possible target organ, although the YM150-related changes observed in the animals were limited to increases in liver enzymes (Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)).

YM150 and YM-222714 showed no potential for genotoxicity, teratogenicity, reproductive toxicity, phototoxicity or skin sensitization. There were no clinically relevant effects in the safety pharmacology core battery tests.

1.2.3.1 High dose 52-week repeated-dose toxicity study in beagle dogs

The results from the 52-week high dose repeated-dose toxicity study in dogs (150-TX-030) are presented in Table 3. Please refer to the current version of the IB for further information.

Table 3: Chronic repeat-dose oral non-clinical toxicity studies

Study	Species, Strain, Dosing	Sex/No./ dose	Doses* (mg/kg/day)	Deaths	Major findings	Study No.
52-week (high dose)*	Dog, beagle Oral, capsule	7M, 7F[1]	0 60 100	1F (Day 160)	Kidney/Urinary changes: ≥60: low urine volume (M), positive urinary protein and glucose; deposition of lipofuscin in proximal tubule 100: ↑ BUN and creatinine (1M) Other changes: ≥60: salivation, abnormal stool color 100: ↓ food consumption and body weight and emaciation (1F)	150-TX-030

*The NOAEL (3 mg/kg/day) has been established in the previously conducted 52-week repeated-dose toxicity study in dogs (150-TX-016); [1] 3 animals were necropsied at 26 weeks.

In the 52-week repeated-dose oral study in beagle dogs (7/sex/group, of which 3/sex/group were necropsied at 26 weeks), YM150 (0, 60 and 100 mg/kg/day) was administered in gelatin capsules once daily for 52 weeks (Study 150-TX-030).

One female dog was found dead on day 160, which was considered, based on the clinical and histopathological observations, to be caused by accidental asphyxiation.

During the dosing period, slight salivation, vomiting, and abnormal stool color were observed in the 60 and 100 mg/kg groups. Compared with the control group, a significantly high total urinary excretion of glucose was noted in males and females in the 60 and 100 mg/kg groups, especially between days 1 and 4 of dosing. Individually, high total urinary excretion of glucose was noted sporadically in males and females during the whole dosing period.

Very slight or slight increase in pigment granules in the proximal tubular epithelium in the kidney were noted in the 60 and 100 mg/kg groups at the end of dosing for 26 weeks or 52 weeks. These pigment granules were Schmorl positive, PAS negative and Berlin blue negative. Therefore, the increased pigment granules were considered to be lipofuscin-like pigment granules.

All changes mentioned above were also noted in the previously conducted 52-week repeated-dose toxicity study in dogs. Slight emaciation, decreases in food consumption and body weight, which were noted at 100 mg/kg, had not been observed in the previous 52-week oral dose toxicity studies in dogs. Additionally, mainly a low urine volume, and high protein at 60 and 100 mg/kg, and high BUN and creatinine at 100 mg/kg were noted.

The No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day was not changed by these findings.

1.2.3.2 Carcinogenicity Studies

Carcinogenicity studies are currently ongoing in two species, mouse and rat (Studies 150-TX-024 and 150-TX-025). The purpose of these studies is to evaluate the carcinogenic potential of YM150 when administered daily via oral gavage to mice or rats for at least 104 weeks. Assessment of carcinogenicity is based on clinical effects (clinical signs,

assessments of body weight and food consumption, and ophthalmic examinations) and clinical and anatomic pathology. Blood is also collected to determine systemic exposure of YM150 and its metabolites. Please refer to the current version of the IB for further information.

Potential Clinical Relevance of Carcinogenicity Studies

In the ongoing 104-week carcinogenicity study in rats tibial fractures in the hind leg were observed in 11 animals (2%) treated with 40 to 300 mg/kg YM150, between Days 107 and 201 of treatment. No histopathological abnormality of bone was observed other than changes resulting directly from the fractures and no alterations in morphology of cortical bone, trabecular bone or epiphyseal plates have been found. In addition, no bone-related findings have been observed in the repeated-dose toxicity and reproductive toxicity studies. However, no fractures were observed in the control animals.

Warfarin, heparin and aspirin unequivocally retard fracture healing, and there is sufficient data from *in vivo* and *in vitro* studies to indicate the same for LMWHs, albeit to a lesser degree. To date, fondaparinux is the only exception to show no negative effects on bone cells function but has only been tested *in vitro* (Lindner 2008). The main limitations surrounding anticoagulants and fracture healing are the distinct lack of clinical studies and the conflicting results from the few heterogeneous *in vivo* animal fracture model studies concerning LMWHs carried out so far. Although a certain anticoagulant agent is likely to affect both animal and human bone through a similar mechanism, rodents have higher rates of bone turnover and heal quicker than humans and are far from an accurate human model. Dose-dependent effects especially cannot be reliably and quantitatively applied to human models. It has also been suggested that rat fracture models do not offer any applicability to human fracture healing. In addition, the carcinogenicity study treatment is started in rats of 5 weeks old, which is comparable to a child of 6-7 years of age, in which the skeletal system is still under development. Therefore it is not known whether the bone findings are relevant for the older subject population that will be treated for ACS, NVAF and VTE. At this moment the relationship between YM150 treatment and bone fractures cannot be excluded, however, it is currently not known whether the bone findings in rats have implications for human use. Therefore, Astellas is currently evaluating the tibia fractures in rats to determine whether there is a causal relationship between YM150 and the findings in bone and if these findings signal a possible risk for humans receiving YM150.

1.2.4 Clinical Safety and Efficacy

To date, 17 clinical trials with YM150 have been completed: 13 Phase I clinical pharmacology studies, 3 Phase II studies in subjects undergoing hip replacement surgery or knee replacement surgery and 1 Phase II study in the prevention of stroke in subjects with NVAF. Phase II studies in subjects undergoing knee replacement surgery or hip replacement surgery, stroke prevention in subjects with NVAF are currently ongoing.

In Japan several studies in subjects undergoing orthopedic surgery, treatment of Deep Vein Thrombosis (DVT) and prevention of VTE in medically ill subjects are planned to start in 2009.

Healthy Volunteers

A total of 510 healthy volunteers have received YM150; doses up to 720 mg/day administered for 7 days and doses up to 360 mg/day for 14 days have been evaluated. YM150 doses up to 720 mg have been safe and well tolerated. The maximum tolerated dose of YM150 has not been reached.

Generally, the safety profile was consistent with that of a healthy volunteer population. The most common adverse events (AEs) in most of the studies included headache and bleeding events of gingival bleeding, epistaxis, or hematoma. Most of the AEs were mild in severity. No deaths occurred, and 1 subject had a serious adverse event (SAE) (hospitalization due to intravertebral disk protrusion). A total of 7 subjects discontinued YM150 due to an AE: 3 subjects discontinued due to bleeding events, 1 subject discontinued due to the flu and 3 subjects discontinued due to cardiac events (hypertension, AF and QT prolongation). The observations leading to discontinuation may not be related to YM150.

There was little change in mean values over time for clinical laboratory parameters, including hematology, serum chemistry and urinalysis. A small number of subjects had renal or hepatic laboratory parameters above the upper limit of normal (ULN) during the studies; most of these increases resolved with continued dosing or during the posttreatment period. In Study 150-CL-028, an increase in mean total bilirubin was observed for all dose groups receiving YM150. The maximum increase in total bilirubin was generally reached on Day 8-10 and returned to baseline at the post study visit.

The safety, tolerability and PD of the combination of 325 mg ASA and 240 mg YM150 have been investigated in healthy volunteers in study 150-CL-034 (also see current version of the IB for YM150). The exposed subjects tolerated the combination well. There was a slightly increased incidence of bleeding events (all minor except one not related AE) in the group receiving the combination. The results of the study further indicate a prolonged skin bleeding time in subjects receiving the combination. YM150 alone did not result in an increase of the skin bleeding time. Moreover the PD parameters FXa activity, platelet aggregation, thromboxane B2, PT and aPTT were not affected by the combination in comparison to either ASA or YM150 alone.

Efficacy in Patients

Two Phase II studies were conducted with YM150 in subjects undergoing elective hip replacement surgery. Study 150-CL-003 was a Phase II, randomized, enoxaparin-controlled, open-label study (Eriksson et al, 2007) and Study 150-CL-008 was a Phase II, multi-center, randomized, double-blind, enoxaparin controlled (administered open-label), parallel group study. YM150 doses of 3, 10, 30 and 60 mg/day administered for 7-10 days once daily were evaluated in Study 150-CL-003 and YM150 doses of 5, 10, 30, 60 and 120 mg/day

administered for 33 to 38 days once daily were evaluated in Study 150-CL-008; the open-label enoxaparin dose in both studies was 40 mg subcutaneously once daily.

A total of 174 subjects were randomized and received at least one dose of study drug in Study 150-CL-003. 960 subjects underwent surgery and received at least one dose of study drug in Study 150-CL-008.

In Study 150-CL-003, the incidence of VTE was assessed at the end of therapy (day 7 to 10) and included DVT proven by bilateral contrast venography within 24 hours after the last dose of study drug, and/or confirmed symptomatic DVT during treatment, and/or non-fatal pulmonary embolism during treatment and/or death due to any cause during treatment. The incidences of VTE during treatment were 51.9%, 38.7%, 22.6%, and 18.5% for the respective YM150 3, 10, 30 and 60 mg dose groups, and 38.7% for the enoxaparin group. A statistically significant decrease in the incidence of the combined VTE endpoint with increasing YM150 daily doses was observed (p=0.006 for subjects reaching the VTE endpoint during treatment; p=0.02 for subjects reaching the VTE endpoint at any time during the study). The incidence in the pooled enoxaparin treated subjects was similar to that of the YM150 10 mg daily group.

In Study 150-CL-008, the primary efficacy endpoint was the rate of total VTE during the 'hospitalization phase' of the study (up to Day 7-10), defined as the composite endpoint of DVT proven by bilateral contrast venography and/or symptomatic DVT, and/or symptomatic PE (pulmonary embolism) and/or death due to any cause during treatment. The overall incidences of VTE at YM150 doses were 27.4% for 5 mg, 31.7% for 10 mg, 19.3% for 30 mg, 13.3% for 60 mg and 14.5% for 120 mg. The VTE rate for enoxaparin was 18.9%. The study results show that the primary analysis trend test in incidence of VTE endpoint over the dose range 5 to 120 mg YM150 was statistically significant (p=0.0002). This trend test was applicable also when a smaller dose range of 5 to 60 mg was taken into account (p=0.0005). There is thus strong evidence of reduced VTE rates at the higher doses of YM150.

Recently an open-label, dose-escalation study in Asian subjects undergoing knee replacement surgery was completed. The preliminary results of this study support the results of the 150-CL-003 study discussed above.

Safety in Patients

AEs reported in the Phase II studies in post orthopedic surgery were commonly observed in this post-surgical population; most were mild to moderate in severity. No clear dose-related trends in AEs were apparent in the YM150 treatment groups. Similarly, no patterns in the incidence or types of AEs in the YM150 groups as compared to the enoxaparin group were observed in the Phase II studies.

Bleeding Events

In Study 150-CL-003, no major and few clinically relevant non-major bleeding events (3 CRNM bleeding events reported in the YM150 3 and 10 mg dose groups) were reported

through the end of therapy (day 7 to 10). No trend with dose of YM150 was observed in the incidence of bleeding events in this study.

In Study 150-CL-008, one treatment-emergent major bleeding (wound bleedings) occurred in a subject in the YM150 60 mg group and in one subject in the enoxaparin group during the hospitalization phase of the study (up to day 10). Clinically relevant non-major bleedings during the hospitalization phase occurred in 1.9% to 4.3% of subjects in the YM150 groups and in 2.4% of subjects in the enoxaparin group (up to day 10). In the YM150 groups, any bleeding event up the end of the study occurred in 3.8%, 5.0%, 7.1%, 10.4% and 12.8% in the 5 mg, 10 mg, 30 mg, 60 mg and 120 mg dose groups, respectively, and 5.4% in the enoxaparin group.

In the recently completed Phase II studies, SAEs in subjects undergoing knee replacement surgery (150-CL-033) or in subjects with NVAF (150-CL-030) were generally consistent with the population under study. A 75-year-old male with AF randomized to YM150 240 mg in the recently completed Asian NVAF study 150-CL-030 died as a result of a brain stem hemorrhage. Additionally, the incidence of clinically relevant non-major bleeds was greater in the YM150 240 mg arm of the study compared with the 30 mg, 60 mg, and 120 mg arms. The DSMB reviewed the safety findings in the study and recommended discontinuation of the YM150 240 mg arm of the study. Sponsor has subsequently removed the 240 mg dose group from the study.

Other AEs, Including Events Leading to Discontinuation

In Study 150-CL-003, the incidence of AEs was similar across the YM150 groups (67%-82%) and the enoxaparin group (72%). Most frequently reported AEs were constipation, diarrhea, nausea, vomiting, pyrexia, incision site hemorrhage, wound secretion, prolonged coagulation time, arthralgia, dizziness, epistaxis, hematoma, hypotension, thrombosis, DVT and wound hemorrhage. There were no deaths in Study 150-CL-003. A total of 10 subjects reported 11 SAEs; none were considered related to study drug. Two subjects discontinued study drug due to an AE (one each in YM150 3 mg and 10 mg groups). Both AEs (nausea and syncope) which led to discontinuation were considered unrelated to study treatment.

In Study 150-CL-008, the incidence of AEs was similar across the YM150 groups (61%-71%) and the enoxaparin group (69%). AEs that occurred in ≥5% of subjects in any treatment group were anemia, nausea, vomiting, hyperthermia, peripheral edema, pain, pyrexia, urinary tract infection, increased Gamma-Glutamyl Transferase (GGT), decreased hemoglobin, hematuria, DVT and venous thrombosis. A total of 3.8% to 9.9% of subjects treated with YM150 and 4.8% of subjects treated with enoxaparin experienced an SAE. A total of 9.6% to 14.9% of YM150-treated subjects and 6.6% of enoxaparin-treated subject discontinued study drug due to an AE. Overall thromboembolic events were the most frequently occurring AEs, leading to discontinuation in all treatment groups. Thirteen subjects receiving YM150 were discontinued from the study due to bleeding events. There were no dose-related trends in the frequency of SAEs or AEs leading to discontinuation. It is not clear whether the open- label nature of enoxaparin administration may have influenced the reporting of AEs.

Renal AEs occurred with similar frequency in all treatment groups; no subject discontinued study drug due to a renal AE.

At the end of the treatment period, mean values for hematology and serum chemistry parameters were within the normal (reference) ranges. No dose-dependent findings and no clinically meaningful differences between YM150 treatment groups and the enoxaparin group were noted.

Shifts from normal to high were seen for hepatic biomarkers in both the YM150 and enoxaparin comparator groups. Mild to moderate transaminase elevations (transient and/or reversible) were common for subjects receiving YM150 and the enoxaparin comparator and occurred more often in the enoxaparin group. Although liver function abnormalities were observed in subjects in the YM150 and enoxaparin groups, abnormalities typically resolved spontaneously under continuous treatment or were resolving. Shifts from normal to high for total bilirubin occurred predominantly among those subjects receiving YM150 and were reversible. These general and mild bilirubin elevations were independent from transaminase elevations.

Six subjects in the 150-CL-008 study (4 in the 10 mg group, 1 in the 60 mg group and 1 in the 120 mg group) developed ALT elevations of >3 times the ULN and concurrent bilirubin elevations of >2 times the ULN. In one of these subjects, the elevation in ALT occurred two days following the bilirubin elevation. In addition one subject in the 3 mg group in study 150-CL-003 had transaminase elevations of > 3 times the ULN with elevations in bilirubin of > 2 ULN in samples drawn 24 hours apart. These 7 patients are subject of a separate evaluation regarding etiology and drug relatedness. Based on the careful ongoing analysis of available data it can be concluded that the risk benefit of YM150 has not changed. No long-term sequelae and no cases of hepatic failure, hepatic encephalopathy, coma, asterixis, or other evidence of severe hepatic failure were observed in these subjects.

One subject randomized to YM150 120 mg with a history of arterial hypertension died due to acute anterior MI. Although the Principal Investigator assessed the death as possibly related to study drug, Sponsor believes that pre-existing risk factors for myocardial ischemia identified prior to dosing may have been contributory to the event.

No AEs strongly suggestive of myocardial ischemia (acute MI, myocardial ischemia, and angina pectoris) were seen in Study 150-CL-003. In Study 150-CL-008, similar rates for treatment-emergent cardiac AEs were found in the combined YM150 dosing cohorts compared to the enoxaparin group.

Fatal Events

In the completed studies, one death occurred in Study 150-CL-008 (YM150 120 mg dosing group) and was attributed to MI. In the ongoing studies, one death due to brain stem hemorrhage occurred in Study 150-CL-030 (YM150 240 mg unblinded dosing group). In the 150-CL-033, a 52 year old female subject experienced an intracerebral hemorrhage and died. The subject was found unresponsive two days after the last dose and discharge from the

hospital. No other deaths have been reported in the YM150 studies for subjects receiving either YM150 or comparator drugs, including placebo.

Pregnancy

Non-clinical safety studies have shown that YM150 has no potential to affect fertility in female rats or to induce embryo-fetal toxicity or teratogenicity in rats or rabbits. Non-clinical distribution studies have shown that placental transfer to fetuses was low after oral administration of YM150 to pregnant rats and that YM150 transfers into breast milk of lactating dams. There is no clinical experience with the administration of YM150 to pregnant women.

Effects on Ability to Drive and Use Machines

The mechanism of action of YM150 suggests that YM150 would not be expected to have an effect on the ability to drive or operate machinery; however, no information is available.

Overdose

Based on the mechanism of action of YM150, an increased bleeding tendency can not be excluded. To date there is no known antidote to the pharmacologic effect of YM150. Supportive measures, such as induction of emesis, can be taken to impede absorption of YM150. In case of clinically relevant bleeding, fresh frozen plasma or packed red cells and other adequate measures can be administered at the discretion of the investigator.

1.3 Summary of Key Safety Information for Study Drugs

Clinical studies to date have shown that the bleeding risk (considered the major safety concern) is small and that such risk appears to be acceptable within the context of thrombosis prophylaxis. The risk of bleeding for YM150 60 mg was comparable to enoxaparin 40 mg with regard to major and clinically relevant non-major bleedings in subjects undergoing elective hip replacement surgery. The incidence of minor bleeding events tended to increase with YM150 dose. The AE profile of YM150 was similar to enoxaparin, and no dose-related AEs were observed.

Mild and transient increases in total bilirubin levels have been associated with treatment of YM150 in both healthy volunteers and patients. These bilirubin elevations were only sometimes accompanied by transaminase elevations.

Transient transaminase elevations (following stopping or on continuation of study drug) were common in the Phase II VTE prevention studies for both YM150 and the enoxaparin control groups. No subjects with transaminase elevations had any symptoms related to hepatic failure.

Increases in serum creatinine concentrations have occurred with similar frequency in YM150 and enoxaparin treated subjects; no events of renal failure have been observed.

The relationship between treatment outcome and both INR and *ex vivo* FXa inhibition will continue to be evaluated in YM150 studies. The relationship between the risk for bleeding and both the INR and FXa inhibition has been evaluated in YM150 studies. The INR and

FXa inhibition does increase with increasing dose of YM150, and individual high values of INR have been seen especially within 1-2 hours after dosing. Analyses of bleeding events, including PK/PD analyses, have shown that the dose of YM150 is the best predictor for risk of bleeding.

The overall safety profile of YM150 appears to be acceptable for VTE prophylaxis following hip or knee replacement surgery as well as in subjects with NVAF at doses up to 120 mg/day. For this study, in subjects presenting with ACS, the selected dose levels of 10 mg daily up to 60 mg daily appear to be acceptable. Subjects may have a clear benefit in reduction of ischemic events during the 6 month treatment period. Since YM150 is added to standard of care with ASA alone or in combination with clopidogrel, there may be a higher risk for bleeding events.

The following AEs have been reported for YM150:

- All bleeding events, except fatal events and bleeding events occurring in critical organs (i.e. intraocular, cerebral, retroperitoneal),
- Blood and Lymphatic System Disorders: Anemia,
- Investigations: Coagulation test abnormal, hemoglobin decreased, INR increased, Liver Function Test (LFT) abnormal, Prothrombin time ratio decreased.

A detailed description of safety information can be found in the latest version of the YM150 IB.

1.4 Risk-Benefit Assessment

The current standard of care for subjects with ACS is ASA, given in a once daily dose up to 162.5 mg with or without clopidogrel in a once daily dose of 75 mg, and all subjects randomized will receive this treatment and are hence optimally treated. The major treatment aim in this indication is prevention of ischemic events, particularly MI and death.

In this study, subjects, who are clinically stable after presenting with a NSTE-ACS or STE-ACS and are treated according to international and local guidelines, will be randomized to receive YM150 in different doses or placebo in addition to the standard of care.

Given the pharmacological effect of YM150 it is hypothesized that addition of a direct FXa inhibitor to existing standard of care of dual antiplatelet therapy will further decrease the risk of MI, stroke and death during the treatment period.

The lowest dose selected for this study may show no added efficacy compared to standard of care, although it is expected that even a relatively low level of FXa inhibition in addition to (dual) platelet inhibition will have clinical benefit.

On the other hand, addition of a FXa inhibitor may result in increased bleeding tendency leading to a higher risk for bleeding events. Previous studies in other indications have established a dose related increase in bleeding events.

The risk for subjects in this study is mainly driven by the increased risk of bleeding. Based on other studies in this indication with other FXa inhibitors, as discussed in the introduction

section, it is expected that the lower dose group of 10 mg daily in this study will have clinical benefit with limited risk for bleeding events. However, the subjects randomized to the higher dose groups may benefit from a greater reduction in risk for MI, stroke and death, but at the cost of bleeding events which may partly offset the clinical benefit. Subjects will be monitored closely for events related to excessive anticoagulation.

Risks of potential clinical interest identified in pre-clinical toxicology studies of YM150 involve myocardial, renal and hepatic systems. However, clinical studies, completed and ongoing to date, have shown only isolated reports of LFT abnormalities, few (ischemic) cardiac events and no renal events. These events were without any dose relationship. YM150 seems to be associated with small increases in bilirubin. This protocol includes monitoring for the development of AEs in these organ systems (regular laboratory measurements and ECGs).

2 STUDY OBJECTIVE(S), DESIGN AND VARIABLES

2.1 Study Objectives

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 with ASA with or without clopidogrel in the secondary prevention of Ischemic Vascular Events in Subjects with recent ACS.

The secondary objectives are:

- To evaluate the efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA with or without clopidogrel in the secondary prevention of Ischemic Vascular Events in Subjects with recent ACS,
- To compare safety, tolerability and efficacy of different doses and dose regimens of YM150 on top of standard treatment with ASA with or without clopidogrel against Placebo,
- To assess PKPD properties in the target population,
- To further define the suitable subject population for further development (i.e. Phase III).

2.2 Study Design and Dose Rationale

2.2.1 Study Design

Current guidelines (Bassand, 2007; Anderson, 2007) advise adjunctive anticoagulant treatment in subjects with STE-ACS or NSTE-ACS for up to 8 days or during hospitalization.

Ximelagatran explored treatment of 6 months while earlier studies with warfarin evaluated treatment up to two years and beyond (Wallentin, 2003; Anand, 1999). Both treatment regimens showed significant reduction of death and ischemic outcome when given in addition to ASA alone.

At the scientific meetings of the ESC and AHA in 2008 results were presented of 6 months treatment with newly developed FXa inhibitors (presentation of APPRAISE and ATLAS TIMI 38). Both studies showed additional benefit of adding an anticoagulant to standard anti-platelet treatment during 6 months albeit at the cost of bleeding events.

Based on the abovementioned observations, it is anticipated that addition of an oral FXa inhibitor for 6 months to standard antiplatelet therapy in subjects with NSTE-ACS and STE-ACS will result in further reduction of ischemic events and death. This study will primarily evaluate whether this regimen is safe and tolerable, and secondary evaluate whether there is additional clinical benefit. The design of the study will also allow for evaluation of the optimal daily dose level and the preferable dose regimen for further studies.

Since the standard of care is antiplatelet therapy for up to one year after the index event all subjects in the study will be treated accordingly and following (local) guidelines.

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

After subjects 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 subjects 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.

Subjects will be screened for eligibility after presentation with the index event.

If considered eligible, once stabilized, subjects 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. Subjects 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 b.i.d.
- Group 2: YM150 10 mg q.d.,
- Group 3: YM150 15 mg b.i.d.,
- Group 4: YM150 30 mg q.d.,
- Group 5: YM150 30 mg b.i.d.,

- Group 6: YM150 60 mg q.d.,
- Group 7: Placebo.

Other antithrombotic drugs given for the initial management of the index event during the acute phase need to be discontinued before study treatment is initiated. Other medical treatment, such as beta blockers, angiotensin II inhibitors and others can be given as per (local) practice and guidelines. See section 5.1.3. for further specification.

During the acute management period, between initial presentation with the index event and randomization subjects will be hospitalized. The screening can be performed when deemed appropriate by the investigator. When the subject is judged as clinically stable by the investigator, the subject can be randomized.

Subjects 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, subjects 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.

After the baseline visit the subjects 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 subject 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 subjects there will be an additional visit/telephone consultation at week 30 after baseline to collect information on the vital status of the subject 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).

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

The study organization will consist of a Steering Committee (SC), an Independent Adjudication Committee (IAC) and an independent Data and Safety Monitoring Board (DSMB).

The SC has contributed in the study design and protocol development and has shared scientific responsibility for the protocol. Moreover, the SC will advise Astellas following recommendations of the DSMB.

A blinded IAC will adjudicate the specified study outcomes centrally.

An independent DSMB will periodically review (un-)blinded data and give recommendations to the SC and Astellas regarding the continuation or termination of a dose group of YM150 or the overall study.

The responsibilities and deliverables of the abovementioned committees will be described in respective charters.

2.2.2 Dose Rationale

Previous studies with YM150 in prevention of venous thromboembolism in subjects undergoing total hip replacement surgery have demonstrated that YM150 30 mg q.d. is an efficacious anticoagulant with an efficacy and safety profile comparable to standard treatment, enoxaparin 40 mg q.d. The lower dose level of 10 mg yielded limited or no efficacy benefit in this indication.

In a recently completed study in Asia, South Africa, Oceania and Japan, subjects with NVAF were treated with YM150 with doses ranging up to 240 mg once daily for up to three months (study 150-CL-030). The independent DSMB have periodically reviewed unblinded data and have not found major safety concerns in doses up to and including 120 mg.

On this background YM150 will be evaluated in the efficacious dose in VTE prevention (i.e. 30 mg daily, one lower dose level of 10 mg daily and one higher dose level of 60 mg daily) in order to define the optimal dose level for this indication. The lower dose level is included because YM150 will be added to (dual) antiplatelet treatment. This will allow evaluation of the addition of a low dose anticoagulant to antiplatelet therapy. The high dose of 60 mg daily will allow evaluation whether further dose increase results in additional safety concerns.

In addition, the dose will be given as once daily (q.d.) and twice daily (b.i.d.) regimens in order to assess the potential benefit of having lower plasma levels throughout the day.

2.3 Variables

2.3.1 Primary Variable

The primary outcome variable is the incidence at six months of Major and Clinically Relevant Non Major (CRNM) bleeding events according to the ISTH definition (Schulman, 2005) and as determined by the IAC.

All overt bleeding events will be reported by the investigator, and adjudicated and classified by the IAC to major, clinically relevant non-major and minor bleeding events. Details on the adjudication process are described in the IAC Charter. The classifications of bleeding events are listed below. All bleeding events will be reported via AE reporting and through specific questions at each visit, and will be sent to the IAC.

2.3.1.1 Major Bleeding

Major bleeding is defined as any of the following:

- Fatal bleeding,
- Clinically overt bleeding associated with a decrease in the hemoglobin level of more than 2 g/dL (1.24 mmol/L) compared with the pre-bleeding level,
- Clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells (see also below on transfusion tracking),

- Symptomatic bleeding in a critical area or organ, such as retroperitoneal, intracranial, intraocular, intraspinal, intraarticular, pericardial or intramuscular with compartment syndrome.

2.3.1.2 Clinically Relevant Non-Major (CRNM) Bleeding

Any bleeding event considered as clinically relevant by the IAC which does not meet the criteria of major bleeding event, e.g.:

- Any bleeding event that requires medical attention,
- Any bleeding requiring discontinuation of blinded study drug treatment.

2.3.1.3 Minor Bleeding

All other bleeding events, which do not fulfill the criteria of major bleeding event or CRNM bleeding event, will be classified as minor bleeding events.

2.3.1.4 Additional Bleeding parameters

Additional bleeding related parameters to be assessed by the IAC include:

2.3.1.4.1 Transfusion Tracking

All transfusions will be documented. The reasons for transfusions will be collected under the following general headings:

- Acute blood loss > 15% of total blood volume (750 mL in 70kg male),
- Acute blood loss resulting in hypotension (diastolic blood pressure (BP) < 60 mmHg, or systolic BP decrease > 30 mmHg from baseline),
- Acute blood loss of any amount in the setting of increased risk of ischemia - pulmonary disease, CAD, cerebral vascular disease, etc.,
- Acute blood loss resulting in organ dysfunction, such as oliguria/anuria and prerenal azotemia,
- Acute blood loss resulting in symptomatic anemia (tachycardia [> 100 beats/minute], mental status changes, angina, shortness of breath, light headedness or dizziness with mild exertion),
- Other reasons as specified by the investigator.

2.3.1.4.2 Calculation of Decrease in Hemoglobin

Decrease in hemoglobin level attributable to the bleeding episode will be documented. This will be calculated by:

- Decrease in hemoglobin + transfused blood (hemoglobin equivalent*).

  **1 unit of packed red blood cells (RBC) = 1 g/dL hemoglobin equivalent.*

The difference between two relevant hemoglobin measurements at stable periods before and after a bleeding episode (within 24 hours after cessation of bleeding) will be calculated. Decrease in hemoglobin level will be calculated by the investigators and recorded in a Bleeding Adverse Event eCRF.

Hemoglobin will be measured as listed in section 5.4.3. The investigator may decide to perform additional hemoglobin measurements, if clinically indicated.

2.3.1.5 TIMI bleeding definitions

For better understanding and to be able to compare to other studies, the bleeding events will be classified separately according to the Thrombolysis in Myocardial Infarction (TIMI) classification (Cannon C, 2001). This classification will not be used for the primary analysis.

The following bleeding categories are defined:

- TIMI Major bleeding events

Major bleeding events are defined as

- Intracranial bleeding or clinically overt bleeding associated with a fall in hemoglobin of greater than 5g/dL from baseline (pre - bleeding level).

Note: Intracranial bleeding will be counted as TIMI Major bleeding event.

- TIMI Minor bleeding events.

Minor bleeding events are defined as:

- Clinically overt bleeding (including bleeding event on imaging studies) associated with a fall in hemoglobin of 3g/dL to less than or equal to 5g/dL from baseline (pre - bleeding level).

2.3.2 Secondary Variables

Secondary Outcome Variables:

- Incidence of Major and CRNM bleeding events at 30 days,
- Incidence of TIMI Major bleeding events at 30 days and 6 months,
- Incidences of composite of all cause mortality, non-fatal MI, non-fatal stroke, severe recurrent ischemia at 30 days and 6 months,
- Incidence of composite of all cause mortality, non-fatal MI and non-fatal stroke at 30 days and 6 months,
- Incidence of individual efficacy variables (all cause mortality, non-fatal MI, non-fatal stroke, systemic thromboembolic event, TIA, severe recurrent ischemia) at 30 days and 6 months,
- Incidence of total bleeding events (major, CRNM and minor bleeding) at 30 days and 6 months,
- Overall tolerability of YM150 (i.e. SAE, AE, changes in laboratory parameters),
- Incidence of composite of all cause mortality, non-fatal MI, non-fatal stroke and Major bleeding events,

2.3.3 Other Variables

- PK/PD assessment of YM150, PD parameters include F1+2, D-dimer and FXa inhibition.

3 STUDY POPULATION

3.1 Selection of Study Population

Male or female subjects with a diagnosis of NSTE-ACS or STE-ACS are eligible for randomization in this study. Diagnosis will be confirmed according to accepted international guidelines as issued by the ESC and the AHA (Bassand, 2007; Anderson, 2007).

Subjects will be managed as per mentioned guidelines and can be screened after presentation of the index event. If eligible, subjects can be randomized as early as possible after clinical stabilization, but within 7 days of presentation of the index event. In total 1264 subjects with NSTE-ACS or STE-ACS as index event will be randomized.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

Inclusion criteria are: male or female subject who:

1. has a diagnosis of STE-ACS, NSTE-ACS as index event according to accepted guidelines such as the ESC or AHA guidelines,
2. has elevated cardiac biomarkers (cardiac Troponin T or I or CK-MB) > 2x ULN for CK-MB or > ULN for troponin,
3. either has STE-ACS, or for subjects with a diagnosis of NSTE-ACS, at least one of the following additional high risk factors for ischemic events must be present:
   - ST deviations on Electrocardiogram (ECG) at any time between presentation of the index event and randomization
   - Age of 65 years or older
   - Previous ACS < 12 months prior to randomization
   - Multi vessel Coronary Artery Disease (CAD)
   - Ischemic stroke or Transient Ischemic Attack (TIA) > 12 months prior to randomization
   - Type 2 Diabetes Mellitus
   - Peripheral Arterial Disease (PAD)
4. is clinically stable which is defined as discontinuation of parenteral antithrombotics and is not likely to require reinstallment of parenteral antithrombotics at time of randomization and receives current standard oral antiplatelet therapy,
5. is able to be randomized within 7 days after presentation with STE-ACS or NSTE-ACS following management to current best clinical practice in the study centre. This may include thrombolysis or primary PCI for STE-ACS, or early invasive strategy (including PCI) for non-STE-ACS subjects. Subjects should be randomized as soon as possible after discontinuation of parenteral antithrombotics,
6. has provided Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations or Informed Consent has been obtained from the legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable),

7. is 18 years of age (legal minimum age required per country) or older at time of informed consent.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

Exclusion criteria at time of randomization are: the subject:

1. requires ongoing parenteral or oral anticoagulant therapy (such as vitamin K antagonists, UFH, low molecular weight heparin (LMWH), fondaparinux, thrombin inhibitors), thrombolytics (such as Tissue Plasminogen Activator (TPA), streptokinase), Glycoprotein (GP) IIb/IIIa antagonists or other antiplatelet drugs (such as cilostazol, ticlopidine, dipyridamole, prasugrel),
2. is planned for myocardial revascularization (e.g., Coronary Artery Bypass Graft (CABG) or elective or staged PCI) or any other invasive procedure with increased risk for bleeding (i.e. elective surgical procedures) within 60 days after randomization,
3. has active bleeding or is in the opinion of the investigator at high risk of bleeding during the study,
4. has had recent stroke or TIA ≤ 12 months prior to index event,
5. has a bleeding diathesis or any other condition or laboratory abnormality with an increased tendency for bleeding (e.g., platelet count below 100.000/uL),
6. is a female of childbearing potential who refuses to use a medically acceptable form of contraception throughout the study. Acceptable methods of contraception include the following: oral or injectable hormonal contraceptives, intrauterine devices, vaginal hormonal rings, and only in combination with a male condom, a vaginal diaphragm or cervical caps. Male study subjects should be advised to use male condom in addition to having their partner use another acceptable method during the study and for three months after the last dose,
7. is a female who is pregnant or lactating or has a positive pregnancy test within 72 hours prior to randomization,
8. has persistent BP of 160 mmHg systolic or higher and/or 100 mmHg diastolic or higher at baseline with or without medication,
9. has hepatic insufficiency or presents with ALT > 2.0 times the ULN or total bilirubin > 1.5 times the ULN (result based on (local) laboratory testing on blood sample drawn within maximally 24 hours prior to randomization),
10. has a renal creatinine clearance of <60 mL/min as calculated by the Cockcroft-Gault equation (result based on (local) laboratory testing on blood sample drawn within maximally 24 hours prior to randomization),
11. has any concurrent illness which, in the opinion of the investigator, may interfere with treatment or evaluation of safety or completion of this study,
12. has participated in another clinical trial of an investigational drug (including placebo) or device within 30 days (or the limit set by national law, whichever is longer) of signing informed consent for the present study,
13. has participated in any YM150 clinical trials,

14. has known allergy to the study drug or any of its components.

3.4 Discontinuation Criteria for Individual Subjects

A discontinuation is a subject who enrolled in the study and for whom study treatment is terminated prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

It is also possible that the sponsor or the competent authorities request termination of the study if there are concerns about conduct or safety in conjunction with the SC and DSMB.

Interruption of blinded study drug is allowed for management of bleeding events other than major bleeding events. This is not a reason for discontinuation of the subject from the study, unless the investigator considers it is in the best interest of the subject. Subjects are allowed to restart double-blind study drug if the bleeding event has subsided. Subjects who experience a major bleeding event as defined in section 2.3.1.1 are to be withdrawn from the study.

Interruption of study drug for PCI

- Interruption of blinded study drug is allowed for subjects who require a PCI, which was not foreseen at baseline. As a reminder, PCI performed as a result of the efficacy endpoints MI or severe recurrent ischemia requires permanent discontinuation of blinded study drug.
- Wherever possible, the investigator must allow a 24-hour wash-out from blinded study drug prior to the administration of other anticoagulants during the PCI. To maintain the blind, a 24-hour wash-out should be observed prior to monitoring coagulation, e.g. activated partial thromboplastin time (aPTT), wherever possible.
- Blinded study drug must be re-started as soon as possible after the PCI, preferably within 24 hours. However, when resuming blinded study drug the minimum time window from most recent antithrombotics (for example LMWH, unfractionated heparin, bivalirudin) included in Appendix 1 must be observed.

Interruption of study drug for minor procedures e.g. dental extraction

Interruption of blinded study drug is allowed for subjects who require minor invasive procedures such as dental extraction. Wherever possible, the investigator should allow a 24-hour wash-out from blinded study drug prior to the procedure. Blinded study drug must be re-started as soon as possible after the procedure, preferably within 24 hours, provided there is no longer an elevated risk of bleeding.

There will be no replacement of withdrawn subjects regardless of the reason of withdrawal.

Discontinuation criteria for individual subjects:

Double-blind study drug must be discontinued permanently if the investigator diagnoses any of the following:

- Major Bleeding event as defined in section 2.3.1.1,
- Stroke or TIA as defined in section 5.3,
- Systemic thromboembolic event as defined in section 5.3,
- MI as defined in section 5.3,
- Severe recurrent ischemia as defined in section 5.3,

Double-blind study drug must also be discontinued if any of the following occur:

- Marked liver enzyme abnormalities (see appendix 3):
  - Concurrent increase of ALT/AST > 3 x ULN AND total bilirubin >2 x ULN
  - Increase of ALT/AST >5 x ULN OR total bilirubin >3 x ULN,
  - When possible, Investigators should confirm marked liver function test abnormalities with a second sample for the central and/or local lab (within 2 to 4 days following the first sample showing the marked increase).
  - Study medication should be stopped if the investigator considers that the subject's condition warrants it (e.g. severely elevated liver function tests) or if it is not possible to obtain a repeat sample within 4 days after the original sample.
- Acute marked increase of ≥ 50% in serum creatinine since the previous visit.

If double-blind study drug is discontinued for any reason, except withdrawal of consent or death, subjects will remain in the study for end of treatment evaluations and complete the 4 weeks follow up period.

The reasons for withdrawal or premature discontinuation will be recorded in the eCRF. Subjects experiencing one of the study endpoints or SAE's will be followed until resolution or until the event is fully characterized.

4 STUDY DRUGS

4.1 Description of Study Drugs

YM150 tablets will be supplied in 5 mg, 10 mg, 15 mg, 30 mg and 60 mg tablets. Placebo to match tablets (PTM) will be provided as described in section 4.1.2.

All subjects will receive three tablets of YM150 and/or PTM day in a double-blind fashion to guarantee adequate blinding of the once daily and the twice daily groups:

- Group 1: YM150 5 mg b.i.d.,
- Group 2: YM150 10 mg q.d.,
- Group 3: YM150 15 mg b.i.d.,
- Group 4: YM150 30 mg q.d.,
- Group 5: YM150 30 mg b.i.d.,
- Group 6: YM150 60 mg q.d.,
- Group 7: Placebo.

The allocation ratio will be 1:1:1:1:1:1:2. Randomization will be stratified by country and by clopidogrel use. Tablets are to be taken orally with adequate liquids (such as water). Subject will receive double-blind treatment with YM150 or placebo for a total duration of 26 weeks.

Subjects will be advised to take the morning study drug (two tablets) at approximately 10:00 a.m. and the evening dose (one tablet) at approximately 10:00 p.m. Subjects will be instructed to record the date and time of each intake of study drug on the wallets containing the study drug.

4.1.1 Test Drug(s)

In this study YM150 is administered as a monomaleate salt. YM150 is available in 5 mg, 10 mg, 15 mg, 30 mg and 60 mg tablets. YM150 5 mg, 10 mg, 15 mg, 30 mg and 30PTM tablets are yellow and have the same size, color and appearance. YM150 60 mg and 60PTM tablets are pink and have the same size, color and appearance.

All investigational materials should be kept in a secured area inaccessible to unauthorized individuals.

4.1.2 Comparative Drug(s)

Placebo to match tablets will be given as reference in the placebo dose group, Group 7. For this purpose, and for the placebo tablets to guarantee adequate blinding of the once daily and the twice daily groups two types of PTM are available. One to match the 5 mg, 10 mg, 15 mg and 30 mg tablets (i.e. 30PTM tablet), and one to match the 60 mg tablets (i.e. 60PTM tablet).

4.2 Packaging and Labeling

All study drug used in this study will be prepared, packaged, and labeled under the responsibility of Qualified Persons at Astellas in accordance with Astellas Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization guidelines for Good Clinical Practice (ICH GCP), and applicable local laws/regulations.

For European centers, the address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding does not need to appear on the label. For these centers, the subject will be given a leaflet or card which provides these details, and the subject will be instructed to keep this in his/her possession at all times.

Study drug for the double-blind treatment period will be packed in kits for 32 days of treatment containing 4 wallets of YM150 and YM150 PTM tablets. Each wallet contains 24 YM150/PTM tablets sufficient for 8 days of double blind treatment.

All Investigational Medicinal Products (IMP) will be labeled according to the requirements as published in Annex 13, version July 2003, of the GMP guidelines. The labels will be approved by a local representative and finally released by the head of quality control. A Qualified Person (from APEB) will release the final IMP according to the requirements of EU Directive 2003/94/EG.

4.3 Study Drug Handling

YM150 and YM150 PTM tablets should be stored at room temperature, but not above 30°C.

The investigator or designee will supply study drug to subjects during the study.

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g., a pharmacist), and that

- Such deliveries are recorded,
- Study drug is handled and stored safely and properly,
- Study drug is only dispensed to study subjects in accordance with the protocol,
- Any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug after approval of the sponsor are followed.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any person except the subjects in this study,
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs,
- A study drug inventory will be maintained by the investigator/pharmacist. The inventory will include details of materials received, and a clear record of when they were dispensed and to which subject,
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

Unused study drug and empty packages may not be destroyed at the study center. Study drug will be returned to the sponsor or a representative after drug accountability has been conducted by the sponsor or a representative. Destruction will take place by the sponsor or a selected third party after written approval of sponsor.

4.4 Blinding

4.4.1 Blinding Method

This is a double-blind, placebo-controlled, randomized, parallel group study. Subjects will be assigned at each site to a double-blind treatment arm. Subjects will receive their allocated treatment according to a computer-generated randomization schedule prepared by the sponsor or sponsor's designee prior to the start of the study.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

This is a double-blind, placebo-controlled study. All subjects will receive YM150 or YM150 PTM to maintain the blind.

YM150 5 mg, 10 mg, 15 mg and 30 mg tablets are identical in size, color and appearance. YM150 PTM tablets will be used in this study. The YM150 30PTM is identical in size, color and appearance to the YM150 5 mg, 10 mg, 15 mg and YM150 30 mg tablets.

YM150 PTM (60 mg) tablet will also be used in this study. The YM150 60PTM is identical in size, color and appearance to the YM150 60 mg tablet.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The sponsor's Drug Safety and Pharmacovigilance (DSP) department has access to the code break information to ensure unblinded Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting to regulatory authorities and ethics committees according to the European Clinical Trial Directive and/or national regulations, if applicable. The staff at DSP keeps the blind for staff at other departments and will communicate only blinded information to the study team.

The investigator can break the treatment code for a subject in exceptional circumstance only. The only acceptable reason for breaking the treatment code is that the information is necessary for medical management of the subject.

4.4.4 Breaking the Treatment Code for Emergency

In the event of a medical emergency requiring knowledge of the treatment assigned to the subject, the treatment code can be broken using Cenduit Interactive Response Technology (C.I.R.T.). The time and date of any code break will be recorded within the C.I.R.T. system, but must also be documented in the study file. A code break will only be authorized for the investigator or other persons duly registered in the study file as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure. The sponsor will be automatically informed in a blinded fashion by the C.I.R.T. system that site staff has broken a study code. The sponsor will inform the DSMB about the reason for breaking the code for a subject. A record of any code break will be available at all times and documented to the sponsor at the end of the study.

Withdrawal of a subject from the study (see section 3.4) is not a sufficient reason to break the study blind. Any decision to break the blind must be discussed with the sponsor in advance, except when such a delay may threaten the well-being of the subject. In this case, the sponsor should be informed as soon as possible after the blind has been broken.

If the blind is broken for a subject, the reason is to be documented as a written entry in the source document. Key information will be recorded at the time when the blind is broken. This includes the date and time when the blind is broken, the reason, the person who requested the breaking of the blind, the name of the person who broke the blind, and the name of the sponsor representative contacted (if applicable).

Any unused study drug for the unblinded subject will be returned to the investigative site for accountability.

Any emergency breaking of the blind by the investigational staff must be immediately reported to the 24 hour-Contact for SAEs (see Section II Contact Details of Key Sponsor's Personnel) and must include an explanation of why the blind was broken.

Unblinding Clinical Studies for Bioanalysis of YM150 and FXa

Bioanalysis of YM150 and FXa will be performed under the responsibility of the Coordinator Bioanalysis of Astellas. Bioanalysis of YM150 and YM-222714 will be done at PRA International (Assen, Netherlands) and the analysis of FXa activity will be outsourced to SGS Cephac (Saint Benoît, France). Separate bioanalytical protocols will be used for the bioanalysis. Samples from subjects who received YM150 will be analyzed to determine YM150 and YM-222714 levels and other metabolites and FXa activity in plasma. The number of samples to be analyzed will be reduced by removing the need for bioanalysis of the samples from subjects receiving placebo by unblinding this study for bioanalytical analysis of YM150, YM-222714 and other metabolites and FXa activity in plasma, i.e. only the samples from subjects who received YM150 treatment will be analyzed. Unblinding of the samples will be carried out according to Astellas procedure. In order to identify which samples should be analyzed, the responsible Study Directors of PRA International and SGS Cephac and the Coordinator Bioanalysis from Astellas will be provided with the randomization code list for this study.

BARC (Gent, Belgium) will analyze prothrombin fragments 1 and 2 and D-dimer. The results of these analyses combined with a subject number will be withheld until after formal unblinding of the study has taken place.

Astellas, PRA International and SGS Cephac will ensure that the staff members, who will be unblinded, will not pass on information regarding treatment assignments in the study, whether informally or formally, to any other person. Bioanalytical results combined with a subject number will only be provided to the Clinical Data Science Department of Astellas after formal unblinding of the study has taken place.

4.5 Assignment and Allocation

Subjects, who meet the inclusion/exclusion criteria, will be randomly assigned to receive either daily oral YM150 (5 mg b.i.d., 10 mg q.d., 15 mg b.i.d., 30 mg q.d., 30 mg b.i.d. or 60 mg q.d.), 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 ASA alone or ASA + clopidogrel). Subjects, who use clopidogrel alone, will be stratified to the ASA + clopidogrel group.

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 subject 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 subjects, the assigned medication identified by kit number and subject number will be provided. Study drug assignment will remain blinded to all staff.

If a subject is assigned a study drug and a subject number, but does not receive study drug, the subject number will not be used again.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

Daily oral doses of YM150 given as 5 mg b.i.d., 10 mg q.d., 15 mg b.i.d., 30 mg q.d., 30 mg b.i.d., and 60 mg q.d. will be investigated and compared with placebo. Table 4 summarizes the type of tablets for each dose group taken at approximately 10:00 a.m. and at approximately 10:00 p.m. Subject will receive double-blind treatment with YM150 or placebo for a total duration of 26 weeks. Each subject will take 2 tablets double-blind treatment at approximately 10:00 a.m. (in the morning) and 1 tablet double-blind treatment at approximately 10:00 p.m. (in the evening) each day. After cessation of double-blind treatment (YM150 or placebo subjects) subjects will enter a 4 week follow-up period.

For visit V5 subjects will be instructed not to take the morning double-blind treatment at home, but will bring the study drug to the investigational site for intake after the first blood samples for PK/PD analysis have been drawn.

Table 4: Number of tablets to be taken per dose group per day

	10:00 a.m. (approximately)							10:00 p.m. (approximately)				
Tablet (mg)	**5**	**10**	**15**	**30**	**30 PTM**	**60**	**60 PTM**	**5**	**10**	**15**	**30**	**30 PTM**
Treatments												
Group 1: YM150 5 mg b.i.d.	1						1	1				
Group 2: YM150 10 mg q.d.		1					1					1
Group 3: YM150 15 mg b.i.d.			1				1			1		
Group 4: YM150 30 mg q.d.				1			1					1
Group 5: YM150 30 mg b.i.d.				1			1				1	
Group 6: YM150 60 mg q.d.					1	1						1
Group 7: Placebo					1		1					1

5, 10, 15, 30 mg YM150 and 30 PTM tablets are indistinguishable from each other ( ), and 60 mg YM150 and 60 PTM are indistinguishable from each other ( ). Each subject will take 2 tablets at approximately 10:00 a.m. (in the morning) and 1 tablet at approximately 10:00 p.m. (in the evening) of each day.

5.1.2 Increase or Reduction in Dose of the Study Drugs

An increase or decrease in dose of double-blind study drug is not allowed. However, it is allowed to temporarily stop double-blind study drug to manage bleeding events, or to allow PCI or minor invasive procedures as described in Section 3.4.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

Previous and concomitant medication will be entered in the concomitant medication electronic case report form (eCRF). All medications taken within 14 days of start of study drug, medications taken during the treatment period and through end of study will be collected.

During the acute management of the index event several antithrombotics can and will be utilized as per standard of care. Subjects 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 UFH need to be stopped at least 2 hours,
- Bivalirudin needs to be stopped at least 2 hours,
- LMWH need to be stopped at least 8 hours,
- Fondaparinux need to be stopped at least 18 hours,
- GP IIb/IIIa antagonists need to be stopped
  - at least 12 hours for abciximab,
  - at least 6 hours for eptifibatide or tirofiban.

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.

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.

For a more detailed list of prohibited and restricted concomitant medications refer to Appendix 1. Drugs other than those listed are permitted.

5.1.4 Treatment Compliance

The investigator or designee will acknowledge receipt of the study drug on forms provided by Astellas or its designee. The investigator will maintain an adequate dated inventory log of drug received from the sponsor and drug issued to and returned by subjects.

Prior to dispensing to a subject, the box(es) containing study drug wallets will be counted. The subject will be instructed to bring all used, partially used and unused wallets of study drug to all study visits, including unscheduled visits.

Returned wallets will be counted to assess subject compliance. All used, partially used and unused wallets of study drug dispensed to subjects will be returned to the investigator. The investigator will return all study drugs to the sponsor, or its designee, accompanied by a completed Return of Investigational Drug Form.

5.1.5 Emergency Procedures and Management of Overdose

There is no experience with the treatment of YM150 overdosing and no known specific antidote for treatment of overdose of YM150. Bleeding is considered to be the greatest concern in the event of overdose. In case of Major Bleeding as defined in section 2.3.1.1 double-blind study drug has to be discontinued permanently.

In case of clinically relevant bleeding, the following actions can be considered:

- Temporary discontinue double-blind study drug until bleeding is under control or resolved. The investigator may also decide to temporary stop antiplatelet treatment, if this is warranted by the subject's condition,
- Standard treatment in case of bleeding, including blood transfusion, fresh frozen plasma or packed red cells and other adequate measures are permitted at the discretion of the investigator,
- Permanently stop study treatment.

The investigator is allowed to temporarily suspend study drug dosing in case of a bleeding event, but no longer than 7 days. If reinstatement of study drug is to be considered following a clinically relevant bleeding event, the investigator must contact the Medical Expert (see section II) prior to reinitiating. If the study drug can not be reinitiated within this 7 day period, the subject has to be withdrawn from the study and the Medical Expert must be contacted.

5.1.6 Restrictions During the Study

Investigators should explain to the subjects the matters to be adhered to by the subject including the dosage regimen and items/procedures of examinations, with specific attention to the following:

- Subjects should take study drug orally with adequate fluids without chewing,

- Subjects should comply with the investigators' directions in taking study drug. If the subject forgets or fails to take the drug at a designated time, intake of two divided doses at the same time is not allowed. The subject should be instructed to take the dose as soon after noticing, but never after noon, for the morning dose and never after midnight for the evening dose,
- To undergo specified examinations, subjects should conform to the clinic visit days designated by the investigators,
- In the case that one or more of the following situations arises or applies, subjects should report such to the investigators: 1) the subject has visited other clinics or departments, 2) the subject needs to receive medications other than the investigational drug during the study period, including over-the-counter (OTC) drugs,
- Female subjects of childbearing potential should use a medically acceptable form of contraception throughout the study. Acceptable methods of contraception include the following: oral or injectable hormonal contraceptives, intrauterine devices, vaginal hormonal rings, and only in combination with a male condom a vaginal diaphragm or cervical caps. Male study subjects should be advised to use male condom in addition to having their partner use another acceptable method during the study and for three months after the last dose.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Date of birth, race and sex are demographic parameters to be documented at the screening visit (V1).

Height will be documented at the baseline visit (V2).

Weight will be documented at V2 and V8/EOT/VD.

5.2.2 Medical History

The following elements of medical history will be recorded at screening: medication history; any adverse reactions to medications; history of hepatic, renal, neurological, endocrine, cardiovascular or pulmonary disease; alcohol consumption; smoking status; prior hospitalization, operations, prior history of cancer and history of other serious illness and conditions involving medications. At baseline visit (V2), any new signs and symptoms recorded since the screening medical history and physical exam, but prior to receiving study drug, should be recorded as AEs.

Medical history pertaining to the presence of risk factors is defined as follows (Betriu, 1998; Cannon, 2001):

- CAD: previous MI or significant coronary lesions (> 50%) at cardiac catherisation and/or previous CABG/PCI,
- PAD: symptoms such as claudication at rest or at exertion, or positive non invasive testing with a ankle brachial index of less than 0.8, or documented with peripheral angiography or history of amputation for arterial vascular insufficiency,

- DM2: history of diabetes, regardless of duration of disease, need for antidiabetic agents, or a fasting blood glucose greater than 7 mmol/L or 126 mg/dL,
- For definition of previous stroke or TIA or MI see section 5.3 below.

In addition, relevant clinical and laboratory information concerning the subject at presentation to the clinic and the acute management need to be recorded.

Particularly the following needs to be recorded:

- Clinical symptoms at presentation (duration of typical symptoms),
- Vital signs at presentation (resting pulse, BP),
- Results of local laboratory assessment at presentation (initial serum creatinine, maximum troponin T/I and/or CK-MB levels,
- Details of ECG at presentation,
- Detailed recording of all antithrombotics given including loading doses of ASA and/or clopidogrel and/or parenteral antithrombotics, daily doses given, duration of treatment, start and stop dates and time,
- Results of angiography, details of access site etc.,
- Details of PCI including stent type (BMS, DES), target vessel(s), number of stents used.

5.2.3 Diagnosis of the Target Disease

A complete medical history of the target disease will be recorded at screening. This includes documenting the history of ACS and the details of acute management of the index event.

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 at 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.

5.3 Efficacy Assessment

Systemic thromboembolic events, MI, severe recurrent ischemia and death will be evaluated by the investigator as per standard of care.

Evaluation of stroke and TIA will be performed by the investigator and a local neurologist or stroke specialist. A Computed Tomography (CT) scan or magnetic resonance imaging (MRI) will be performed when a subject presents with a stroke, TIA or systemic thromboembolic event.

All events will be adjudicated by an IAC. Descriptions of the events will be sent to the IAC for evaluation. The assessment of the events by the IAC will be recorded in the Adjudication eCRF. Summary data will be reported to the DSMB, SC and sponsor. All subject data submitted to the IAC will be kept blinded with regards to treatment allocation and dose.

Additionally, while stroke, TIA, systemic thromboembolic event, MI , severe recurrent ischemia and death are considered efficacy variables, these events will be considered in characterizing the safety profile of YM150 as well. Specifically, a hemorrhagic stroke will be classified and counted once as a major bleeding event.

Due to the nature of ACS as a high morbidity and mortality disease, the efficacy endpoints (TIA, systemic thromboembolic event, MI, and severe recurrent ischemia) are not to be reported as SAEs (see Section 5.5.2). .

Death

Death will be adjudicated by the IAC and categorized as:

- Cardiovascular death
- Non-cardiovascular death (only where a there is a known cause which is clearly non-cardiovascular in origin).

Further sub-categorization will be defined in the Adjudication Charter.

(Non Fatal) Myocardial Infarction (MI)

MI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria will meet the diagnosis for MI (Thygesen, 2007):

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia,
- ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)],
- Development of pathological Q waves in the ECG,
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

The criteria for the diagnosis of an MI will be described in the Adjudication Charter. MI will be categorized as follows (Thygesen, 2007):

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 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 CABG.

(Non Fatal) Stroke

Stroke is defined as the abrupt onset of a focal neurological deficit in the distribution of a cervical (carotid or vertebral) or cerebral artery persisting for greater than 24 hours. Stroke will be classified as hemorrhagic, non-hemorrhagic or unknown. A hemorrhagic stroke will be counted once as a major bleeding event.

Disabling Stroke

Disabling stroke will be adjudicated based on the score on the modified Rankin scale at 30 days or at hospital discharge (following hospitalization for stroke) whichever comes first. Disabling stroke is defined as a score of 3 or more on the modified Rankin scale evaluation.

Transient Ischemic Attack (TIA)

TIA is defined as the abrupt onset of a focal neurological deficit in the distribution of a cervical (carotid or vertebral) or cerebral artery persisting for less than 24 hours.

Systemic Thromboembolic Event

Systemic thromboembolic event is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion, in the absence of other likely mechanisms (i.e., atherosclerosis). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolic event requires the angiographic demonstration of abrupt arterial occlusion.

Severe Recurrent Ischemia

Severe recurrent ischemia is defined as worsening anginal symptoms lasting at least 10 minutes and associated with at least 2 of the following: dynamic $\geq$ 0.1 mV ST depression

or elevation, hospitalization, or unplanned cardiac catheterization with evidence of significant coronary stenosis.

5.4 Safety Assessment

The following measurements will be collected to evaluate safety: physical examination; ECG; vital signs; laboratory measurements; specifically bleeding events and (S)AEs. The DSMB will periodically review ongoing study data to monitor for any safety concerns during the study.

5.4.1 Vital Signs

Vital signs, including blood pressure and pulse rate, will be assessed at all visits. Blood pressure should be taken after subject has been sitting quietly for approximately five minutes.

In addition, resting pulse and blood pressure recorded at presentation of the index event will be entered into the eCRF at screening.

5.4.2 Adverse Events

AEs will be assessed regularly during the study and will be collected from the time the informed consent form is signed until the end of the study including the FU visit.

All observed or spontaneously reported AEs will be recorded in the electronic case report form (eCRF). If a diagnosis is made from the signs and /or symptoms, the diagnosis should be recorded in preference to the listing of individual signs and symptoms. If no diagnosis can be made, the investigator should record each sign and symptom as an individual AE.

Data to be recorded include a description of the event, dates of onset and end of the event, intensity, seriousness, action with respect to study drug, treatment required, relationship to study drug and outcome of the event. See section 5.5 for further details.

5.4.3 Laboratory Assessments

Pregnancy Test

Pregnancy tests will be done locally during the study.

Urine pregnancy tests for female subjects of childbearing potential will be done at visit V2, V6 and FU visit. A pregnancy test will not be required if female subject is ≥ 2 years postmenopausal.

Local Laboratory Analysis

Local laboratory results of serum creatinine and cardiac enzymes at presentation of the index event and as measured during the study at the discretion of the investigator will be recorded. It is advised to repeat troponin or CK-MB every six hours for up to at least 12 hours after presentation of an ischemic cardiac event in order to capture the peak values.

A blood sample for local laboratory results for ALT, total bilirubin and creatinine required at baseline in order to assess eligibility for randomization should be taken within 24 hours prior to randomization. Local test results should be recorded in the eCRF.

For adjudication of specific events of interest, such as liver enzyme increases and renal dysfunction, results of local laboratory tests if available will be recorded in addition to central laboratory results as detailed below.

Hematology, Chemistry and Urinalysis

A central laboratory will analyze the hematology, chemistry and urinalysis.

Central laboratory samples for hematology, chemistry and urinalysis will be taken on all visits except V1 and V3. Samples will be analysed for:

- Hematology: hemoglobin, hematocrit, RBC count, white blood cell (WBC) count, differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count,
- Chemistry: sodium, potassium, chloride, calcium, inorganic phosphorus, creatinine, ALP, AST, ALT, GGT, lactate dehydrogenase, total bilirubin, direct bilirubin, indirect bilirubin, albumin, BUN, glucose, total cholesterol (only at V2) and triglycerides (only at V2),
- Urinalysis: (microscopic) leucocytes, erythrocytes; (quantitatively) protein, glucose, creatinine.

In case of a clinically overt bleeding episode, a blood sample to analyze hemoglobin should be taken within 24 hours after the cessation of bleeding. The sample should be forwarded to the central laboratory for further analysis.

5.4.4 Physical Examination

Complete physical examinations will be performed at all visits except V1 and V3. A complete physical examination will include the following: an examination of the skin, including general appearance; neck (including thyroid); eyes; ears; nose; throat; lungs; heart; abdomen; musculoskeletal; neurologic exam and any additional assessments needed to establish baseline status or evaluate symptoms or AEs.

5.4.5 Electrocardiogram (ECG)

A 12-lead ECG will be recorded (using a sponsor-provided ECG machine) at all visits except V1 and V3 (if applicable).

All tracings will be read locally by the investigator to ensure subject safety and care management, and transferred electronically to a central ECG reader. The central ECG reader will provide an independent reading, and the investigator and study team will be informed about abnormal findings. All abnormal ECG findings suggestive of ischemic events will be forwarded to the Independant Adjudication Committee (IAC).

Any time a subject experiences possible cardiac symptoms 12-lead ECGs should be obtained, preferably using the sponsor-provided ECG machine. A copy of each unscheduled ECG will be provided as part of the source documentation of the event that warranted the unscheduled ECG. In addition, the unscheduled ECG recordings should be transferred electronically, or if not otherwise possible, as a copy on paper to the central ECG reader.

If necessary, i.e. in case of abnormal ECG findings suggestive of an ischemic event, a copy of the unscheduled ECG will be sent to the IAC. The event is expected to be reported as an AE or SAE as described in section 5.5. Printouts of all ECGs have to be stored in subject's source data.

5.4.6 Imaging

MRI/CT scans, ultrasound, angiograms, X-rays or any other imaging for diagnosis of systemic thromboembolic event, bleeding and ACS will be sent to the IAC for evaluation.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms,
- Requires active intervention,
- Requires interruption or discontinuation of study drug,
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Any untoward medical occurrence occurring after the informed consent is signed, but prior to the start of study drug, should be recorded as an AE. An AE observed after starting administration of the study drug is called a "treatment emergent adverse event (TEAE)".

AEs will be collected from the time the ICF is signed up until the follow-up visit.

5.5.1.1 Adverse Events of Special Interest

5.5.1.1.1 Liver

As described in the introduction, increases in liver transaminases and total bilirubin were reported in previous clinical studies with YM150. Increases in liver laboratory tests will be monitored carefully in this study and managed according to the monitoring procedures for liver monitoring as described in Appendix 3. Concurrent increases on ALT and/or AST of > 3 x ULN AND total bilirubin > 2 x ULN should be reported as an SAE. However, SAE reporting is not required for concurrent increases at baseline provided that the ALT is ≤ 3 x ULN and any AST elevation is considered to be of cardiac origin by the investigator.

Moderate and marked increases in liver laboratory tests are defined in Table 5.

Table 5: Definitions of liver laboratory abnormalities

	ALT or AST		Total Bilirubin
Moderate	>3 x ULN	or	> 2 x ULN
Marked	>3 x ULN	and	> 2 x ULN
	>5 x ULN	or	> 3 x ULN

5.5.1.1.2 Kidney

As discussed in the introduction section, there is some evidence of a potential effect of YM150 on the kidney in two animal species. In clinical studies temporary postoperative changes in serum creatinine and urine protein were reported albeit at the same frequency as the comparator drug in those studies. Based on the above, YM150 can be regarded as safe and well tolerated, however, further monitoring in Phase II studies is warranted. In this study the following definitions are used pertaining to the degree of change in kidney function:

- Moderate kidney function abnormalities are defined as an increase exceeding 25% in serum creatinine compared to baseline for chronic changes and to previous visit for acute changes,
- Marked kidney function abnormalities are defined as an increase exceeding 50% in serum creatinine compared to baseline for chronic changes and to previous visit for acute changes.

The monitoring of kidney abnormalities is described in Appendix 3.

5.5.2 Definition of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe),
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In addition, sponsor has identified adverse events that should be regarded as "Always Serious". This list is provided in Appendix 4. These events always need to be reported as SAEs independent of the criteria for seriousness as described above.

If a subject becomes pregnant during treatment, this should be reported as if it were an SAE. Refer to section 5.5.7.

The efficacy endpoints in this study (TIA, systemic thromboembolic event, severe recurrent ischemia and MI) could be regarded as Suspected Unexpected Serious Adverse Reactions SUSARs. As such these would need to be unblinded and reported expeditedly.

Due to the nature of ACS as a high morbidity and mortality disease this carries the risk of structural unblinding of important efficacy events related to the disease. In line with the European Community (EC) guidance ENTR/CT 3, these efficacy endpoints which are disease related will not be regarded as SUSARs or SAEs and will not be subject to systematic unblinding and expedited reporting. These events are therefore not to be reported as AEs. Information on these efficacy endpoints will be collected on specific worksheets for adjudication and for DSMB reporting (see Section 5.3). The DSMB will regularly review all efficacy endpoints and all SAEs and AEs reported in the study in order to ensure appropriate evaluation of safety of the subjects in the study.

The efficacy endpoints "non-fatal Stroke" and "Death" however will need to be reported as SUSAR/SAE.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out."

Table 6: Criteria for Causal Relationship of adverse events

Causal Relationship to the Study Drug	Criteria for Causal Relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of AE, including abnormal clinical laboratory values:

- Mild: No disruption of normal daily activities,
- Moderate: Affect normal daily activities,
- Severe: Inability to perform daily activities.

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the delegated CRO by telephone or fax immediately (within 24 hours of awareness or at the earliest possible time point).

The investigator should complete and submit an SAE Worksheet, containing all information that is required by the Regulatory Authorities, to the delegated CRO by fax immediately (within 24 hours of awareness or at the earliest possible time point). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone (for delegated CRO contact details, see the SAE reporting section in the Investigator's Site File).

If contacting or faxing to the delegated CRO is not possible or fails, sponsor contact details can be used: For contact details see Section II Contact Details of Key Sponsor's Personnel. Please fax the SAE Worksheet to:

- Astellas Pharma Europe BV, Drug Safety and Pharmacovigilence Dept.,
  Fax number: +31 (0)71 545 52 08

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Director/Expert or his/her designee (see Section II for contact information).

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

The sponsor or sponsor's designee will submit expedited safety reports (i.e. IND Safety Reports) to the regulatory agencies (i.e. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

You may contact the sponsor's Medical Director/Expert for any other problem related to the safety, welfare, or rights of the study participant (subject/patient).

Full details of the SAE should also be recorded on the medical records and on the SAE CRF page.

All correspondence on SAEs must be marked URGENT. The following minimum information is required:

- International Study Number (ISN)/Study number
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

All SAEs reported up to 4 weeks after the last intake of the study drug should be reported. SAE's and events of interest such as renal dysfunction and hepatic enzyme changes need to be followed until resolution or full characterization.

The sponsor or sponsor's designee will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs, which require submission to their IRB/IEC the head of the study site within timelines set by regional regulations (by MHLW, European Clinical Trial Directives or FDA).

The heads of the study sites/investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

For SUSAR from a blinded trial, unblinded CIOMS-I report will be submitted to the authorities and IRB/IEC where required.

5.5.6 Follow-up to Adverse Events

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized (all follow-up results are to be reported to the sponsor or delegated CRO).

Since it is unpredictable how long such a follow-up will take, data from this follow-up generated after the subject's post study visit will be recorded by the investigator. Full details regarding this follow-up will be described in the study report, whenever necessary.

If during adverse event follow-up, the case has progressed to the level of "SAE", or if a new SAE, whose relationship to the study drug(s) could not be ruled out, is observed, the situation must be reported immediately by the investigator becoming aware of the information.

As described earlier, stroke needs to be evaluated at discharge or 30 days after the occurrence of the stroke, whichever comes first, in order to determine the degree of disability.

After double-blind study drug is discontinued subjects are followed for another four weeks. All adverse events and changes in concomitant medication needs to be reported and recorded in the eCRF. In addition, for premature discontinuation subjects there will be an additional visit/telephone consultation at week 30 after baseline to collect information on the vital status of the subject and on AEs corresponding to efficacy endpoints (death, MI, severe recurrent ischemia, stroke, systemic thromboembolic event and transient ischemic attack).

5.5.7 Procedure in Case of Pregnancy

If a woman becomes pregnant during the study dosing period or within 15 days from the discontinuation of dosing, the investigator should report the information to the sponsor /

delegated CRO as if it was an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the mother as well as the fetus concerned as if it is an SAE and report the outcome to the sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator,
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at birth.
- "Normality" of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

If during the conduct of this clinical study, a male subject impregnates his partner, the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to Astellas.

5.5.8 Supply of New Information Affecting the Conduct of the Study

When new information, including "Dear Doctor Letters" but not limited to that, necessary for conducting the clinical study properly, will lead to a protocol amendment, the sponsor should inform regulatory authorities, as well as all investigators involved in the clinical study, who will then inform the IRB/IEC of such information, and when needed, should amend the subject information.

5.6 Test Drug Concentration

For the purpose of evaluation of population PK, blood samples (4 mL EDTA tubes each) will be obtained from all subjects. Five blood samples per subject will be collected for PK purposes during three visits in total.

One sample will be collected as a random PK sample on V4 (day 14).

Two samples will be collected in the morning at V5 (week 6), and two samples will be collected in the afternoon at V7 (Week 18).

V4: a PK sample will be taken as part of the visit. This will be at a random time in relation to the study drug intake that day. The time of study drug intake (morning and evening) on the

previous day and the time of study drug intake on the morning of V4 should be recorded in the eCRF.

V5: this visit should be scheduled as a morning visit. Subjects should not have taken their morning dose of study drug at home (subject will be reminded of this at their prior V4 visit). At the clinic, one pre-dose blood sample for PK should be collected, after which the subject takes his /her study drug. A second sample is collected 1 – 2 hours after study drug intake. The time of study drug intake (morning and evening) on the previous day and the time of drug intake at the study site should be recorded in the eCRF.

V7: this visit should be scheduled in the afternoon. Subjects should have taken their morning dose of study drug as normal. At the clinic one blood sample for PK should be collected between 13:00 and 17:00. A second blood sample should be collected at around 30 minutes later. The time of study drug intake (morning and evening) on the previous day and the time of study drug intake on the morning of V7 should be recorded in the eCRF.

The investigator can decide to perform the morning sampling at V7 if deemed more practical for the subject. In that case the afternoon sampling needs to be performed at V5.

An unscheduled PK sampling can be performed at V6 if the sample at V5 is missed for any reason.

Please see Investigator's Manual of BARC Laboratories for sampling and handling instructions. All plasma samples should be stored frozen at -20°C and will be shipped frequently (i.e. monthly) to BARC Laboratories, Ghent, Belgium.

YM150 and its metabolite (YM-222714) will be analyzed from each subject receiving YM150 by PRA International B.V., Assen, The Netherlands, using a validated LC-MS/MS method.

When considered necessary, plasma samples may be subjected to metabolite analysis and/or profiling and identification studies, which will be described in a separate (bioanalytical) study protocol. The report(s) for the metabolite analysis and/or profiling and identification will not be incorporated in the integrated clinical study report.

5.7 Other Measurements, Assessments, or Methods

5.7.1 Pharmacodynamic assesments

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 subjects. Blood samples for assessment of F1+2, D-dimer and FXa inhibition will be collected at seven time points during five visits in total.

Samples should be collected at Baseline (V2), visit V4, visit V5, visit V7, and at the FU visit. On the time points for PK sampling (V4, V5 and V7) the samples for F1+2, D-dimer and FXa inhibition need to be taken together with the PK samples in order to allow for PK/PD analysis and modeling. At V5 and V7 two PD samples will be drawn (see section 5.6).

Please see Investigator's Manual of BARC Laboratories for sampling and handling instructions. All plasma samples should be stored frozen at -20°C and will be shipped frequently (i.e. monthly) to BARC Laboratories, Ghent, Belgium.

Analysis of F1+2, and D-dimer will be performed at BARC Laboratories, Ghent, Belgium.

Analysis of FXa will be performed at SGS Cephac, Saint Benoît Cedex, France, using a validated chromogenix assay.

5.7.2 Pharmacogenomic analysis

As recently presented by Mega (Mega, 2009) polymorphisms of cytochrome P450- 2C19 are relevant predictors of clopidogrel activity.

One blood sample will be taken at baseline to specifically analyze 2C19 polymorphisms. The remainder of the sample will be stored for further analysis in the future for other relevant polymorphisms or biomarkers not known to date to be of importance for the assessment of efficacy and safety of antiplatelet therapy or YM150. Samples will be coded in such a way that individual data cannot be traced back to individual subjects. Subjects will be asked specifically to consent for the analyses of 2C19 polymorphisms and separately for the storage of blood for future analysis as detailed above.

5.7.3 Health Economic assessments

To justify the cost of new drugs, decision-makers need to determine not only whether a drug has a statistically significant impact on the clinical endpoint and/or on HRQoL, but they also need to evaluate whether the improvement is meaningful. As part of this Phase II study we will conduct Cost-utility Analysis (CUA) in order to compare YM150 and placebo in terms of their incremental cost per quality adjusted life years (QALY) (i.e. the extra cost of YM150 over placebo divided by the extra QALY gain). In this study placebo entails standard of care with oral antiplatelet therapy.

In addition, Resource Use Inventory will be collected via the standard eCRFs to allow a comparison of the additional cost of managing subjects in the various treatment arms.

QALYs incorporate both length of life and quality of life into a single metric, and are calculated by summing the time periods individuals spend in different health states, weighted by the qualities of the health states. Because new therapies are typically more expensive than standard therapies, CUA has gained prominence as a method to inform decision makers who seek to compare the tradeoff in incremental costs and gains in health conferred by new treatment choices within and across disease states.

To calculate QALYs, it is necessary to present health on a scale where death and full health are assigned values of 0 and 1, respectively. Therefore, states rated as better than dead have values between 0 and 1, and states rated as worse than dead have negative scores which, in principle, are bounded by negative infinity.

For the purpose of CUA, QALY weights based on societal rather than subject preferences have been recommended because economic evaluation is usually supposed to support societal

decisions about the allocation of resources provided by the general population (Weinstein MC, 1996). These weights are typically established using utility measurement techniques such as Standard Gamble (SG) and TTO (Brazier J., 1999; Green C, 2000). The EQ-5D index represents societal preference values for the full set of 243 EQ-5D health states with the state '11111' (perfect health) and 'death' being assigned values of 1 and 0, respectively.

A research team at the University of Sheffield in collaboration with Dr. JE Ware of New England Medical Center has estimated a preference-based single index measure of health from the SF-36 (Brazier J, 2002). The index is estimated via a health state classification, called the SF-6D, derived from the SF-36 and is composed of six multi-level dimensions of health. It was constructed from a sample of 11 items selected from the SF-36 to minimize the loss of descriptive information and defines 18,000 health states. A selection of 249 states, defined by the SF-6D, have been valued by a representative sample of the UK general population (n=611), using the SG valuation technique. Like the EQ-5D, regression models were estimated to predict single index scores for all health states defined by the SF-6D. The resultant algorithm can be used to convert SF-36 data at the individual level to a preference-based index.

Two questionnaires will be used to assess the subjects' health status: the EQ-5D (including the visual analogue scale [EQ-VAS]) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).

The EQ-5D is an international standardized non-disease specific (i.e. generic) instrument for describing and valuing health status (Brooks R, 1996). It is a multi-dimensional measure of Health-Related Quality of Life (HRQoL), capable of being expressed as a single index value, or utility score, and specifically designed to complement other health status measures.

The EQ-5D questionnaire comprises five questions (items) relating to current problems in the dimensions 'mobility', 'self-care', 'usual activities', 'pain/discomfort', and 'anxiety/depression' (Brooks R, 1996; The EuroQol Group, 1990). Responses in each dimension are divided into three ordinal levels coded (1) no problems, (2) moderate problems, (3) extreme problems. This part, called the EQ-5D self-classifier, provides a five-dimensional description of health status, which can be defined by a five-digit number. For example, the state '11122' indicates no problems in mobility, self-care, and usual activities, but moderate pain/discomfort and moderate anxiety/depression. Theoretically, $3^5 = 243$ different health states can be defined. The EQ-5D self-classifier is followed by a visual analogue scale (EQ-VAS), similar to a thermometer, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ VAS records the respondent's self-rated valuation of HRQoL (i.e. an index of HRQoL), which is based on the respondent's preferences (EQ-VAS score).

The 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; (2) role limitations due to physical health problems; (3) bodily pain; (4) social functioning; (5) general mental health, covering psychological distress and well-being; (6) role limitations due to emotional problems; (7) vitality, energy, or fatigue; (8) general health perceptions (Ware JE, 1994).

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).

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

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

5.8 Total Amount of Blood

The maximum amount of blood to be taken from a subject according to the scheduled assessments will be approximately 162 mL. In Table 7 an overview has been made to indicate for how much, how often and for what purpose blood will be drawn.

Table 7: Overview of blood samples

Hematology	8 x 3 mL EDTA tube
Biochemistry	8 x 5 mL serum tube
Glucose	8 x 2 mL glucose tube
Pharmacodynamic Assessment	7 x 3 x 2.7 mL citrate tube
Test Drug Concentration	5 x 4 mL EDTA tube
Pharmacogenomic sample	1 x 5 mL whole blood sample
TOTAL	161.7 mL

6 TERMINATION OF THE CLINICAL STUDY

The sponsor reserves the right to discontinue the study at any time for failure to meet expected enrollment goals.

1. When the sponsor becomes aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator.
2. If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

3. An independent Data and Safety Monitoring Board (DSMB) will review efficacy and safety data as it becomes available during the study and may at any time recommend terminating one or more treatment arms or the whole study.

7 STATISTICAL METHODOLOGY

This double-blind, placebo-controlled, randomized, parallel group study is designed to:

- Identify the appropriate total daily dose (10 mg, 30 mg or 60 mg) of YM150,
- Identify the appropriate dose frequency (once daily or twice daily),
- Compare each dose-regimen of YM150 with placebo, in subjects with recent ACS and standard treatment in the secondary prevention of ischemic vascular events.

The statistical analysis will be coordinated by the study biostatistician of the sponsor. A Statistical Analysis Plan (SAP) and table listings and figures specifications will be written to provide details of the analysis. The SAP will be finalized and signed before database lock. Any deviations from the SAP will be justified in the clinical study report.

Shortly before the database is locked, all problematic cases, where evaluation remains unclear, will be scrutinized in a Blinded Data Review Meeting. Consequences for the statistical analysis will be discussed, if necessary.

7.1 Sample Size

158 subjects will be randomized to each YM150 dose group and 316 subjects to the placebo group, for a total of 1264 subjects 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 subjects 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, other 10% of subjects are expected to be censored after the first month, so they will contribute in 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.

7.2 Analysis Set

7.2.1 Full Analysis Set (FAS)

All randomized subjects who took at least one dose of study drug will be included in the Full Analysis Set (FAS).

7.2.2 Per Protocol Set (PPS)

All randomized subjects who took at least one dose of study drug and who did not have any major protocol violations will be included in the Per Protocol Set (PPS). The details about

major protocol violations will be specified in the SAP. All efficacy and PD analyses will also be performed on the PPS.

7.2.3 Safety Analysis Set (SAF)

All randomized subjects who took at least one dose of study drug will be included in the Safety Analysis Set (SAF), which is the same as the FAS.

7.2.4 Pharmacokinetics Analysis Set (PKAS)

All subjects who received at least one dose of study drug, who have values of drug concentration for at least one time point and for which the date and time of dosing and sampling is recorded will be included in the Pharmacokinetics Analysis Set (PKAS). Some subjects may be excluded from this analysis set, if confounding factors might affect the PK results (including protocol violations and deviations). The details about reasons for exclusions will be specified in the PK analysis plan.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized, using descriptive statistics for each randomization arm, and grouped by treatment, regimen and YM150 daily dose.

7.4 Analysis of Efficacy

The cumulative risk (both at day 30 and at month 6) will be provided for all efficacy-related secondary events described in section 2.3.2 and for each randomization arm (and grouped by treatment, regimen and daily dose), using Kaplan-Meier estimates.

The estimated cumulative risk function versus time, using Kaplan-Meier estimates, will be plotted for each randomization arm (and grouping by treatment, regimen and daily dose).

All mentioned estimates will be provided also by stratifying for standard antiplatelet treatment (ASA or ASA + 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 efficacy endpoints.

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.

In order to assess the homogeneity of results in subpopulations, the mentioned Cox regression model will be repeated for each secondary efficacy event and 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 analysis 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. Homogeneity of results may be studied also in other subgroups. Further details will be given in the SAP.

7.5 Analysis of Safety

7.5.1 Analysis of Primary Variable

7.5.1.1 Primary analysis

The primary safety variable, incidence of Major and CRNM bleeding events (ISTH definition) at six months, will be summarized calculating the cumulative risk both at day 30 and at month 6 for each randomization arm (and grouped by treatment, regimen and daily dose) using Kaplan-Meier estimates. The estimated cumulative risk function versus time, using Kaplan-Meier estimates, will be plotted for each randomization arm (and grouping by treatment, regimen and daily dose).

This variable will be inferentially analyzed using a Cox regression model, including YM150 regimen (once daily or twice daily) and the total daily dose adjusted for standard antiplatelet treatment (ASA or ASA + clopidogrel). Subjects who use clopidogrel alone will be stratified to the ASA + clopidogrel group.

The HR and its 95% confidence interval (CI) will be presented for:

- YM150 dose trend (represents the expected increase of risk when YM150 dose is doubled),

7.5.1.2 Secondary analysis

Secondary comparisons for the primary variable will include:

- The HR of incidence rates for 30 mg and 60 mg per day versus 10 mg per day (total daily dose fitted as class factor),
- Test of the total daily dose by regimen interaction, using a similar model as above and adding interaction terms,
- The HR of incidence rates for each of the six YM150 arms with placebo.
- YM150 twice daily against YM150 once daily.

The analyses of the primary variable will be repeated including country in the model if the number of events allows. Countries may be pooled if the number of events is low; pooling will be finalized prior to unblinding. The analyses of the primary variable will also be repeated including time from Index Event to first intake of study drug as covariate.

7.5.1.3 Subgroup Analysis

Primary analysis will be provided for the full population and stratified by standard antiplatelet treatment (ASA or ASA + clopidogrel (including clopidogrel only)).

In addition, in order to assess the homogeneity of results in several subpopulations, the Cox regression model for the primary analysis will be repeated within each subpopulation. HR will be calculated and reported using a forest plot. The variables that will be used to define these subpopulations analysis 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 part of the initial

management. Homogeneity of results may be studied also in other subgroups. Further details will be given in the SAP.

7.5.2 Analysis of Secondary Variables

For all secondary safety events described in section 2.3.2, the cumulative risks and cumulative risk function versus time 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.

7.5.3 Analysis of Other Variables

7.5.3.1 Adverse Events

- All AEs will be listed
- SAEs will be listed separately
- The number and percentage of subjects with at least one treatment emergent AE will be presented
- The number and percentage of subjects with at least one treatment related AE will be presented
- The number and percentage of subjects with at least one AE, as classified by System Organ Class (SOC) and Preferred Term (PT), will be presented
- The number and percentage of subjects with at least one treatment emergent AE, as classified by SOC and PT, will be presented.
- The number and percentage of subjects with at least one treatment related AE, as classified by SOC and PT, will be presented.

7.5.3.2 Vital Signs

- The vital sign data will be listed
- Summary statistics of vital sign data will be presented by treatment group for each time point
- Changes from baseline in vital sign data will be presented by treatment group for each time point.

7.5.3.3 Physical Examination

- Physical examination data will be listed
- Physical examination data will be summarized by treatment group for each time point
- Shifts in the findings from baseline to post-baseline will be presented for each treatment group for each time point.

7.5.3.4 Electrocardiogram (ECG)

- The 12-lead ECG recording data will be listed
- Summary statistics of ECG data will be presented by treatment group for each time point
- Shifts in ECG data from baseline to post-baseline will be presented for each treatment group for each time point.

7.5.3.5 Laboratory Assessments

- The laboratory assessment data will be listed.
- Summary statistics of the laboratory assessment data will be calculated by treatment group for each evaluation time point.
- Changes from baseline in continuous laboratory data will be presented by treatment group for each time point.
- Shifts in categorical laboratory data from baseline to post-baseline will be presented for each treatment group for each time point.

7.6 Analysis of Pharmacokinetics

The plasma concentration data of YM-222714 collected will be subjected to a population PK analysis. For this analysis the data might be combined with results of other Phase II and Phase I studies. The aim of this analysis is to develop a compartmental model of the YM-222714 plasma concentration versus time profiles, which will provide a good estimation of the exposure (AUC) and the inter-subject and intra-subject (if possible) variability in the exposure. In addition, the effects of selected covariates on the clearance will be evaluated (e.g., sex, age, race and body size). Population PK modeling of the plasma concentration data of YM-222714 will be performed using the Nonlinear Mixed Effects Model (NONMEM) software package (version V.1 or higher) or MONOLIX (free software dedicated to the analysis of non linear mixed effects models). During model development SAS (version 9 or higher) or S-PLUS (version 6.0 or higher) will be used for preparing data sets and for graphical and statistical analysis. Information regarding the PK analysis will be described in the separate population PK analysis plan. The results and the model development will be described in detail in a separate population PK report.

7.6.1 Concentration-Response Relationship Analysis

The relationships between plasma concentration of YM-222714 and PD effect (FXa, D-Dimer and Protrombin Fragment 1+2) will be investigated. Initially effect will be plotted against plasma concentration to explore any relationship between the two variables. If applicable, PK-PD models (e.g., linear, log-linear, maximal effect or sigmoidal maximal effect models and link models) will be fitted to the data. Due to the exploratory nature of this analysis the exact model to be used (if any) can not be defined at this stage, but will be decided upon as the data are analyzed.

The details will be described in a separate PK-PD analysis plan, with the model development and results in a separate PK-PD modeling report.

7.7 Other Analyses

7.7.1 Analysis of Pharmacodynamics

The results of the PD analysis will be analyzed as described in section 7.6. Results of D-dimer and F1+2 will also be summarized separately and presented in the study report using descriptive statistics.

7.7.2 Analysis of Health Economic assessments

Health economics and outcomes analyses will be conducted in this study. Resource use inventory will be collected via the standard eCRFs to allow a comparison of the additional cost of managing subjects in the various treatment arms. Meanwhile, subject reported outcomes (PROs) will be derived from 3 sets of questionnaires to be administered to the subjects. All analyses of Health Economic Assessments will be performed on the FAS. In order to evaluate the robustness of the results, the same analyses will be performed on the PPS.

7.7.2.1 EQ-5D

This is a generic instrument that permits the elicitation of utility scores associated with the benefits of treatment effects in the various arms of the study. These scores are subsequently used in the estimation of the cost-effectiveness, or cost per QALYs of the different treatment options.

The five questions of the EQ-5D questionnaire (‘mobility’, ‘self-care’, ‘usual activities’, ‘pain/discomfort’, and ‘anxiety/depression’) will be described by treatment group for each evaluation time point using absolute and relative frequencies for the responses (1= no problems, 2= moderate problems, 3= extreme problems). The visual analogue scale included in this questionnaire will be summarized by treatment group for each evaluation time point using descriptive statistics. This will be also performed stratifying for standard antiplatelet treatment (ASA or ASA + clopidogrel).

7.7.2.2 SF-36

The total score of the SF-36 and the score for the 8 subdomains will be summarized by treatment group for each evaluation time point using descriptive statistics. The change from baseline to endpoint in the total score of the SF-36 will be analyzed using analysis of covariance including dose frequency (once daily or twice daily), logarithm of total daily dose (for placebo, zero on the log scale will be used), gender, country as class variables and baseline as covariates. The difference of means and its 95% CI will be presented for a) YM150 dose trend (represents the expected increase in the score when YM150 dose is tripled or doubled); b) YM150 once daily versus YM150 twice daily; c) 30 mg and 60 mg per day versus 10 mg per day; d) each of the six YM150 dose regimens versus placebo.

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

Ongoing review of safety data will be completed by an independent DSMB (see section 10.1).

A DSMB charter, a DSMB SAP and tables manual will be written to provide details of this analysis.

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

Details in handling missing data, outliers, visit windows, etc. will be specified in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained on submission.

The investigator or designee will enter data collected in an eCRF using an Electronic Data Capture (EDC) system.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

For screening failures, the minimum demographic data (sex, age and race) and reason for failure to randomize will be collected in the Screening Failure Log (SFL) if applicable. This information will be entered into a screening failure database.

Central laboratory tests will be performed at BARC. Central laboratory data will be transferred electronically to the Data Management Center at predefined intervals during the study. The laboratory will provide the Data Manager with a complete and clean copy of the data, accompanied by a Quality Control statement at the completion of the study.

ECG recordings performed at the site will be transferred electronically to a central ECG reader for evaluation. The results of the central read will be sent to the Data Management Center at predefined intervals during the study. The central ECG reading facility will provide the Data Manager with a complete and clean copy of the data, accompanied by a Quality Control statement at the completion of the study.

An IAC will evaluate specified study outcomes centrally and record their findings in an eCRF. The IAC review will focus on bleeding AEs, systemic thromboembolic events, MI, severe recurrent ischemia, TIA, stroke and deaths. The specific method(s) for data collection and data transfer are defined in a separate charter.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study (e.g., medical records, worksheets and nurse records), as well as the medical treatment and medical history of the subject (e.g., relevant medical records from other departments and/or hospitals, or discharge letters and correspondence with other departments and/or hospitals).

The following information should be included in the source medical records:

- Demographic data (age, gender, race/ethnicity, weight, and height),
- Inclusion and exclusion criteria details,
- Participation in the study and signed and dated ICF,
- Visit dates,

- Medical history and physical examination details,
- Key efficacy and safety data as specified in the protocol,
- Relevant information about AEs and concomitant medication,
- Results of relevant examinations,
- Laboratory printouts,
- Dispensing and return of study drug details,
- Reason for premature discontinuation,
- Subject number,
- Study drug allocation numbers,
- Method of contraception for female subjects or subject's partner of childbearing potential.

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subjects' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to section 8.1.2) when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be coordinated by the Clinical Data Science Department of the sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. eCRF retrieval and correction process will be referenced in the eCRF instructions. Coding of medical terms will be performed using MedDRA.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA)

The study must start only after receipt of a written approval from the IRB/IEC, which operates according to ICH-GCP guidelines, and/or from Competitive Authorities (CA), according to the national laws. The written IRB/IEC and/or CA approval and the names and

qualifications of members of the IRB/IEC must be made available to the sponsor before the study can start. The investigator is responsible for submission(s) to, and communications with, the IRB/IEC and CA, if applicable. Documents to be submitted to the IRB/IEC and CA may differ per committee as a consequence of local requirements and guidelines.

If locally required, the investigator shall make accurate and adequate written progress reports to the IRB/IEC at appropriate intervals, not exceeding 1 year. If locally required, the investigator shall make an accurate and adequate final report to the IRB/IEC within 1 year after last patient out (LPO) or termination of the study.

8.2.2 Ethical Conduct of Study

The investigators and all parties involved in the study should conduct the study in accordance with this protocol, in adherence to ICH-GCP Guidelines, the European Clinical Trial Directive and the local applicable laws and regulations. The investigators and the sponsor will sign the protocol and study contract, to confirm agreement. The investigators will not implement any amendment (deviation or changes of the protocol) without agreement by the sponsor and the IRB/IEC and CA approval.

Records that may reveal the identities of subjects must be well protected, with consideration given to confidentiality and the right to privacy of subjects.

Consideration of the subjects' rights, safety and well-being is regarded as the most significant issue and has a higher priority than the scientific and social benefits of the study.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

Prior to execution of the clinical study, the responsible investigator should prepare the written ICF and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and CA, if applicable.

The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.

- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance with the rules at the study site concerned.
- Informed consent must be obtained by the time that the first observations/examinations of the pre-investigational period are performed. Guardian consent should be obtained from the proxy consenter, before start of pre-investigational period.

- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
  - No subject may be subjected to undue influence, such as compulsory enrollment into a study.
  - The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor, auditor and inspector upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator/sub-investigator should immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study or not.
2. If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to 1), the written information should be revised immediately based on the newly available information, and be re-approved by the IRB/IEC.
3. The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in paragraph 2) even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name. The investigator or other responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the first informed consent.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subjects' privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study, according to local laws and regulations.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective study site only after allowing the sponsor to review all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure for APEB-sponsored studies. This is necessary to prevent premature disclosure of trade secrets or patent-protected information and is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following documents:

- Study protocol (and amendments, as applicable),
- Investigator's Brochure (and amendments, as applicable),
- eCRFs and SAE Report Worksheet,
- Investigator's File,
- Study drug with all necessary documentation,
- Study contract,
- Approval of regulatory authority and all documents related to submission.
- IMPD (to be submitted only to competent authorities (CA) in the European Community)

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54,
- Signed and dated FDA form 1572, if conducted under a U.S. IND,
- Investigator submission letter to the IEC,
- Signed confidentiality agreement,
- Signed Investigator's Statement in this protocol,
- Executed Study Contract,
- IEC/IRB approval of the protocol, protocol amendments (if applicable) and ICF (and separate authorization form, if appropriate), stating clearly the sponsor's name, study number and study drug, including a membership list with names and qualifications,
- Current Curricula Vitae of all investigators (signed and dated, brief and in English),
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee),
- Medical/Laboratory/Technical procedures/tests certifications or accreditations or established quality control or other validation, where required.

At the end–of-the study, the sponsor is responsible for the collection of:

- Unused study documentation,
- Unused study drug.

The investigator will archive all study data (e.g. Subject Identification Code List, source data, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulations. The investigator agrees to obtain the sponsor’s agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system (eCRF) or any combination thereof.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data (e.g., eCRF).

The investigator shall report to the sponsor or sponsor's representative(s) any SAEs or deaths during the study, whether regarded as drug-related or not.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study, which arise after approval of the protocol, must be documented as protocol substantial amendments and/or administrative changes/non-substantial amendments. Depending on the nature of the amendment and/or revision, either IRB/IEC and/or CA approval or notification is required. The changes will become effective only after the

approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be agreed upon in writing between the investigator and the sponsor. Written verification of IRB/IEC and/or CA approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC and CA approval, but will be submitted to the IRB/IEC and CA for their information.

If there are changes to the ICF, written verification of IRB/IEC and/or CA approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

8.3.4 Insurance of Subjects and Others

Astellas Pharma Europe B.V. has covered this study by means of an insurance of the subject according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Investigator Indemnity

The sponsor agrees to, and does hereby, indemnify, defend and hold the investigator harmless from and against all claims, demands, actions, and proceedings which may be brought or asserted against the investigator to recover damages and losses for or attributable to bodily injury, sickness, disease, or death arising from or alleged to arise from or be reasonably attributable to this study.

Notwithstanding the foregoing, the sponsor does not, however, agree to indemnify, defend or hold the investigator harmless from claims, demands, actions, proceedings or damages resulting or claimed to have resulted from:

- Failure of the investigator to evaluate or properly interpret available information that is relevant to this study, and for independent decisions made as the result of such failure;
- Failure of the investigator to adhere to all provisions of the protocol for this study and to written recommendations and written instructions delivered to the investigator by the sponsor concerning the administration and use of drug substances, including the placebo, involved in this study;
- Failure of the investigator to render professional service or to conduct this study in a normal, prudent manner.

A condition of this indemnity obligation is that, whenever the investigator has information from which it may be reasonably concluded that an incident of bodily injury, sickness, disease or death has occurred, the investigator shall immediately give notice to the sponsor of all pertinent data surrounding any such incident, and, in the event a claim is made or a suit is brought, the investigator shall assist the sponsor and cooperate in the gathering of information with respect to the time, place, and circumstances and in obtaining the names

and addresses of the injured parties and available witnesses. The investigator shall not, except at his own cost, voluntarily make any payment or incur any expense in connection with any such claim or suit without the prior written consent of the sponsor.

8.3.6 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EMEA Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by a Coordinating (principal) Investigator. The Coordinating Investigator will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. A Coordinating Investigator will be selected from the participating investigators by Astellas prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites. The auditor is independent from the clinical monitoring and project management team at the sponsor. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data and Safety Monitoring Board (DSMB)

An independent DSMB is established. It consists of three members (including an experienced biostatistician), none of whom is involved in the clinical study. The DSMB will review all unblinded safety data concerning AEs, bleeding complications, thromboembolic and cardiac events of all subjects on a regular basis and will meet every two months or more often if deemed appropriate. The DSMB organization, operating and unblinding procedures is described in a separate DSMB charter. The DSMB makes recommendations to the SC and to the sponsor on whether to continue, discontinue or modify the study. The DSMB can request and review data from this and other YM150 studies, to have a more complete overview of safety.

10.2 Other Evaluation Committees

10.2.1 Independent Adjudication Committee (IAC)

An IAC will evaluate the specified study outcomes centrally in order to standardize interpretation and classification of events. The committees will consist of members of appropriate expertise who are not directly involved in the clinical study. The IAC review focuses on four groups (Bleeding AEs, Stroke, Systemic Thromboembolic Events, Cardiac

Events, and death). The IAC will be kept blinded about treatment assignment and dose for the duration of the study. The IAC organization and operating procedures are described in a separate charter.

10.2.2 Steering Committee

A SC, consisting of therapeutic area experts and non-voting representatives from the sponsor, participates in study design and protocol development and will advise sponsor regarding the continuation or termination of a dose group of YM150 or the overall study, based on the recommendation of the DSMB. The final decision on discontinuation of the study or treatment arms or modification of the study protocol lies with the sponsor.

The SC will make recommendations based on available blinded data. The SC organization and operational procedures are described in a separate charter.

10.3 Other Study Organization

Not applicable

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12 APPENDICES

Appendix 1: LIST OF EXCLUDED AND RESTRICTED PREVIOUS AND CONCOMITANT MEDICATION

During the acute management of the index event several antithrombotics can and will be utilized as per standard of care. Subjects 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 UFH need to be stopped at least 2 hours,
- Bivalirudin needs to be stopped at least 2 hours,
- LMWH need to be stopped at least 8 hours,
- Fondaparinux need to be stopped at least 18 hours,
- GP IIb/IIIa antagonists need to be stopped
    - at least 12 hours for abciximab,
    - at least 6 hours for eptifibatide or tirofiban.

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.

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

Thrombolytics

Alteplase, Ancrod, Anistreplase, Brinase, Drotrecogin alfa, Fibrinolysin, Protein C, Reteplase, Saruplase, Streptokinase, Tenecteplase, Urokinase.

Antiplatelet agents

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

Anticoagulants

Vitamin K antagonist: Acenocoumarol, Clorindione, Dicumarol (Dicoumarol), Diphenadione, Ethyl biscoumacetate, Phenprocoumon, Phenindione, Tioclomarol, Warfarin.

Heparin group: Antithrombin III, Bemiparin, Dalteparin, Danaparoid, Enoxaparin, Heparin, Nadroparin, Parnaparin, Reviparin, Sulodexide, Tinzaparin.

Direct Thrombin Inhibitors: Argatroban, Bivalirudin, Desirudin, Hirudin, Lepirudin, Dabigatran.

Others: Fondaparinux, Defibrotide, Dermatan sulfate.

Appendix 2: LABORATORY TESTS

Cental laboratory

	Visit	Collecting tube	Parameters to be analyzed
Hematology	All visits, except V1	EDTA tube 3 mL	Hemoglobin Haematocrit Erythrocytes (RBC) Leukocytes (WBC) Differential WBC Platelets
Biochemistry	All visits, Except V1	Serum tube 5 mL	Sodium Potassium Calcium Chloride Inorganic phosphorus BUN Creatinine ALP AST ALT GGT LDH Total bilirubin Direct and Indirect bilirubin Total protein Total cholesterol (only V2) Triglycerides (only V2) Albumin
Biochemistry	All visits, Except V1	Glucose tube 2 mL	Glucose
PD	V2,V4,V5, V7	Citrate tube 2.7 mL	Prothrombin fragment 1+2, D-dimer, FXa
PK	V4,V5, V7	EDTA tube 4mL	YM-222714 and YM150
Pharmacogenomics	V2	Whole blood tube 5mL	CYP2C19 polymorphisms Future analyses
Urinalysis Quantitative/microscopic	All visits, Except V1	Urine sample	Protein Glucose Creatinine Erythrocytes Leucocytes

Local laboratory

	Visit	Collecting tube	Parameters to be analyzed
Biochemistry	V1	Serum tube(s)	Creatinine (at presentation) Troponin T or I, or CK-MB (max value to be recorded)
Biochemistry	V2	Serum tube	ALT, Creatinine, total bilirubin
Pregnancy tests	V2,V6,FU	Urine sample	Pregnancy test

Appendix 3: LIVER AND KIDNEY SAFETY MONITORING

Definition of liver abnormality

Moderate and marked liver function abnormalities are defined as follows, where ULN:

	ALT or AST		***Total Bilirubin***
Moderate	*>3 x ULN*	*or*	*> 2 x ULN*
Marked	*>3 x ULN*	*and*	*> 2 x ULN*
	>5 x ULN	*or*	*> 3 x ULN*

Baseline Requirement

Baseline values should be consistent with inclusion and exclusion criteria.

Monitoring Procedures

Specific alerts will be generated by the central lab regarding every moderate and marked liver abnormality to inform the investigator, study monitor and study team. Subjects will then all be followed as defined below specified for liver abnormalities.

Marked abnormalities in hepatic functions need to be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests.

Further details on monitoring procedures for marked abnormalities will be provided separately in the "Instructions for Investigators".

Liver

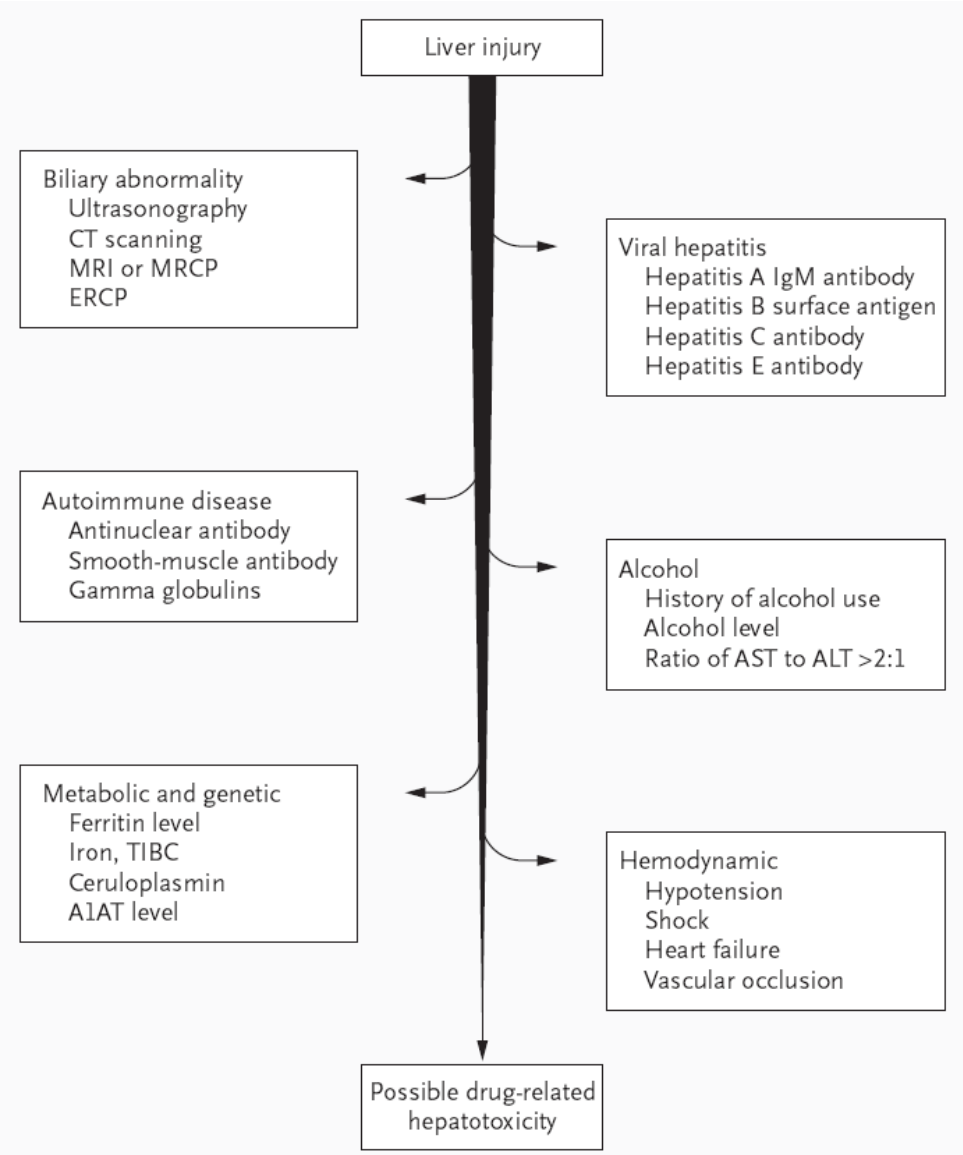
Moderately abnormal LFTs should be repeated after 2-4 days. Moderately abnormal LFTs are thereafter to be followed up weekly until resolved to normal range or until they become chronic as judged by the investigator and consistent with the underlying cause.

A marked increase should be confirmed with repeat testing within 2 to 4 days of the first sample showing the marked increase. Blood samples for the central and/or local lab should be taken and analyzed for at least the following: ALT, AST, ALP, and total bilirubin, direct bilirubin and indirect bilirubin and gamma GT.

The instructions for the investigator and the site are:

- *The site ensures to call the subject to return for a repeat sample preferably within 2 days but ultimately within 4 days after the first sample with the marked abnormalities was drawn. It is required to obtain a blood sample for central laboratory assessment. The site may also obtain a sample for local laboratory assessment in addition.*
- *Based upon repeat, confirmatory sample results of the central laboratory, study drug should be discontinued if:*
  - ALT/AST >3xULN and total bilirubin >2xULN
  - ALT/AST >5xULN or total bilirubin >3xULN
- *The investigator may also decide to discontinue study drug based upon the results of the local laboratory and decide not to wait for the results of the central laboratory. The criteria for discontinuation of study drug are the same as mentioned under the previous bullet point.*
- *If it is not possible to obtain a repeat sample within ultimately 4 days after the original sample, study drug should be discontinued and follow-up samples for central lab are to be collected 2-4 days after the site receives initial notification of the abnormalities.*
- *The investigator may discontinue study drug at any time if he considers that the subject's condition warrants it (e.g. severely elevated liver function tests).*

The subject should have weekly additional visits until the hepatic test changes have resolved to normal range or until they become chronic as judged by the investigator and consistent with the underlying cause. The approach to evaluating liver changes follows the recommendations of Navarro and Senior (N Engl J Med 2006; 354:731-9) as exemplified in the following diagram:



Results of tests and investigations related to this decision tree will be requested (for marked and moderate cases) when relevant in collaboration between investigator, monitor, study team and external hepatic expert. All marked cases will also be adjudicated by the hepatic expert.

Definition of kidney abnormality

Distinction should be made between acute changes in kidney function and chronic changes. The following definitions pertain to the ***degree of change*** *in kidney function. The management plan for changes in kidney function should take into account the acuteness or chronicity of the event as described under "Monitoring procedures".*

- *Moderate kidney function abnormalities are defined as an increase exceeding 25% in serum creatinine compared to baseline for chronic changes and to previous visit for acute changes.*
- *Marked kidney function abnormalities are defined as an increase exceeding 50% in serum creatinine compared to baseline for chronic changes and to previous visit for acute changes.*

Monitoring Procedures – Kidney

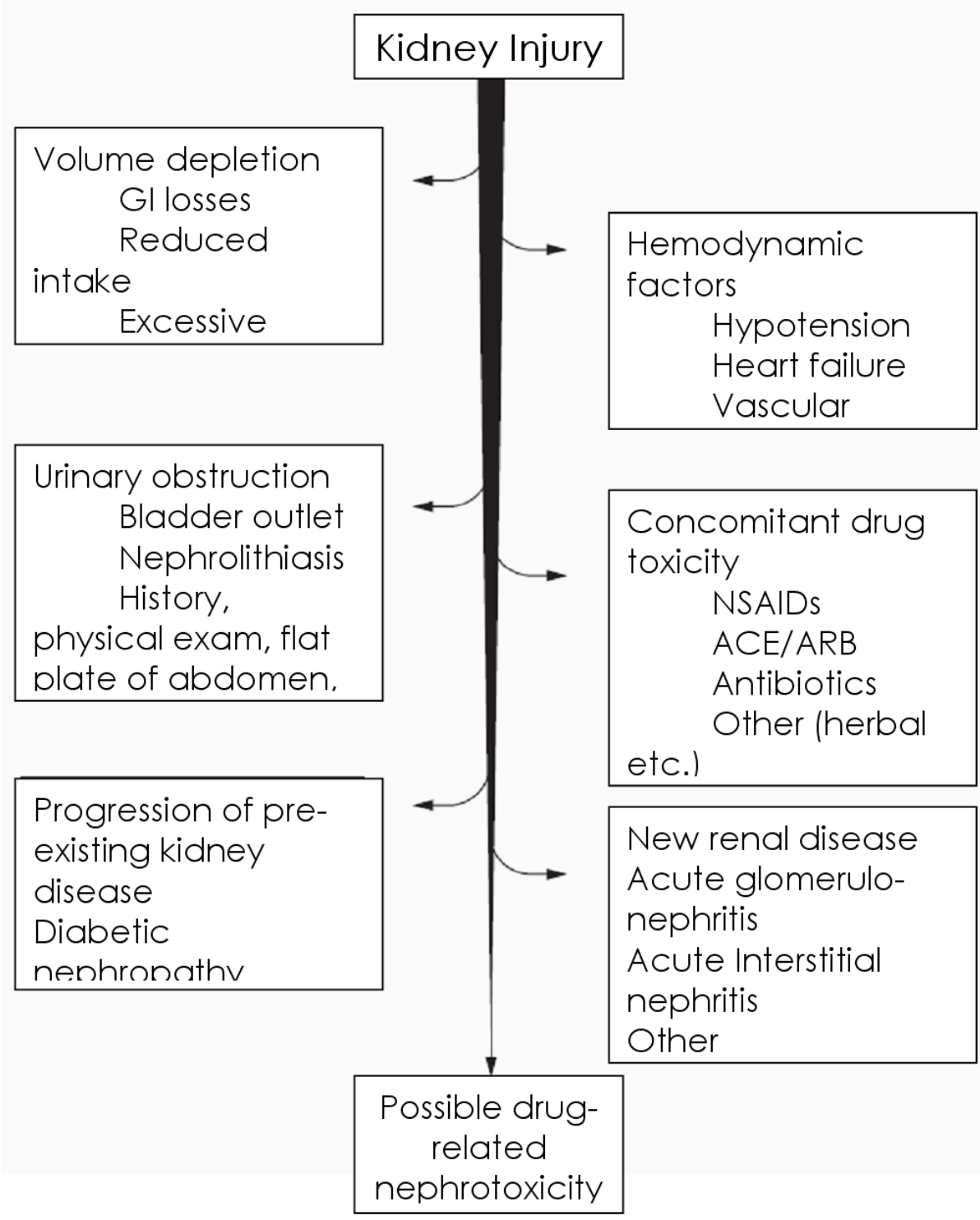
Subjects with ***marked*** *kidney abnormalities should be evaluated thoroughly by the principal investigator in consultation with the Medical Expert and by obtaining timely expert consultation. Subjects with* ***moderate*** *kidney abnormalities should be evaluated by the principal investigator in consultation with the Medical Expert and local expert consultation obtained as needed. The time course of the development of kidney abnormalities should be carefully evaluated and the following approach undertaken:*

- *Subjects with* ***acute marked kidney function abnormalities*** *defined as exceeding 50% increase in serum creatinine since previous visit must discontinue treatment and undergo an evaluation of kidney function within 2-4 days. These changes denote the possibility of acute kidney injury and evaluation for reversible acute factors should be part of the assessment (e.g., hemodynamic instability, volume depletion, acute drug toxicity etc.). Evaluation should continue until it is determined that the patient has returned to his/her previous level of renal function or has stabilized at a new steady state level.*
- *Subjects with* ***acute moderate kidney function abnormalities*** *defined as exceeding 25% increase in serum creatinine since previous visit must undergo an evaluation of kidney function within 2-4 days. These changes denote the possibility of acute kidney injury and evaluation for reversible acute factors should be part of the assessment (e.g., hemodynamic instability, volume depletion, acute drug toxicity etc.). If changes appear to be progressing during the evaluation period, discussion with the Medical Expert regarding continuation of the patient in the study is encouraged. Evaluation should continue until it is determined that the patient has returned to his/her previous level of renal function or has stabilized at a new steady state level.*
- *Subjects with* ***non-acute marked kidney function abnormalities*** *defined as exceeding 50% increase in serum creatinine from baseline value must undergo an evaluation of kidney function within 5-7 days. These changes denote the possibility of either acute kidney injury or chronic changes in kidney function. Evaluation for reversible acute factors should be part of the assessment (e.g., hemodynamic instability, volume depletion, acute drug toxicity etc.), but considerations of chronic changes such as due to*

underlying kidney disease (e.g., diabetic nephropathy) should also be entertained. Discussion with the Medical Expert regarding continuation of the patient in the study is required as the change in renal function may have impact on clearance of study drug. Evaluation should continue until it is determined that the patient has returned to his/her previous level of renal function or has stabilized at a new steady state level, or the changes are determined to be due to an underlying renal disease independent of the study drug.

- *Subjects with* ***non-acute moderate kidney function abnormalities*** *defined as exceeding 25% increase in serum creatinine from baseline value must undergo an evaluation of kidney function within 5-7 days. These changes denote the possibility of either acute kidney injury or chronic changes in kidney function. Evaluation for reversible acute factors should be part of the assessment (e.g., hemodynamic instability, volume depletion, acute drug toxicity etc.), but considerations of chronic changes such as due to underlying kidney disease (e.g., diabetic nephropathy) should also be entertained. If changes appear to be progressing during the evaluation period, discussion with the Medical Expert regarding continuation of the patient in the study is encouraged. Evaluation should continue until it is determined that the patient has returned to his/her previous level of renal function or has stabilized at a new steady state level, or the changes are determined to be due to an underlying renal disease independent of the study drug.*

Further details on monitoring procedures for kidney abnormalities will be provided separately in the "Instructions for Investigators".


Kidney Injury
Volume depletion
GI losses
Reduced intake
Excessive
Hemodynamic factors
Hypotension
Heart failure
Vascular
Urinary obstruction
Bladder outlet
Nephrolithiasis
History, physical exam, flat plate of abdomen.
Concomitant drug toxicity
NSAIDs
ACE/ARB
Antibiotics
Other (herbal etc.)
Progression of pre-existing kidney disease
Diabetic nephropathy
New renal disease
Acute glomerulo-nephritis
Acute Interstitial nephritis
Other
Possible drug-related nephrotoxicity

Appendix 4: ALWAYS SERIOUS TERMS LIST

- Congenital anomalies
- Acute Respiratory Failure
- Ventricular Fibrillation
- Torsades de Pointe
- Malignant Hypertension
- Seizure
- Agranulocytosis
- Aplastic Anemia
- Toxic Epidermal Necrolysis
- Liver Necrosis
- Acute Liver Failure
- Anaphylaxis
- Acute Renal Failure
- Sclerosing Syndrome
- Pulmonary Hypertension
- Pulmonary Fibrosis
- Confirmed or Suspected Transmission of Infectious Agent by Marketed Product
- Confirmed or Suspected Endotoxin Shock
- Malignancy, all terms

Appendix 5: COCKCROFT-GAULT EQUATION

For men:

$$\text{Creatinine Clearance} = \frac{(140\text{-Age}) \times \text{Weight in Kg}}{72 \times \text{Serum Creatinine (in mg/dl)}}$$

For women:

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

To convert serum creatinine from µmol/l to mg/dl, divide the creatinine value by 88.4

Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.

Appendix 6: ELEMENTS OF INFORMED CONSENT

Please note: For information only. An informed consent form will be made available to the study sites

A. Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonable foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records. Note: If subject data will be transmitted via electronic data capture, it is recommended that the informed consent include a statement noting that data collection may be done using a validated electronic data capture system.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subjects is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subjects is otherwise entitled.

B. Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to an embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

Appendix 7: THE EQ-5D HEALTH QUESTIONNAIRE

Health Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

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 ❑

Usual Activities (*e.g. work, study, housework, family or leisure 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 ❑

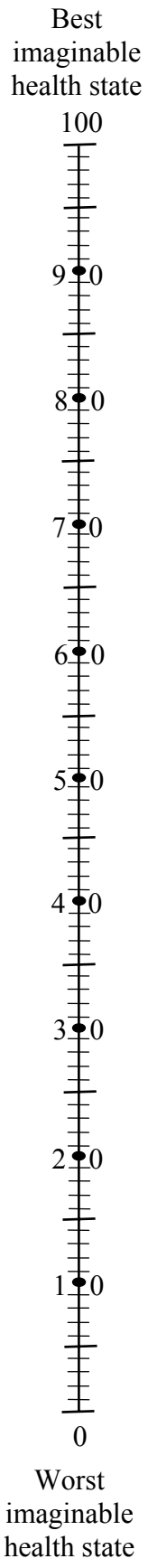
Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.



We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Appendix 8: THE SF-36 HEALTH QUESTIONNAIRE

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
A	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
B	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
C	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
D	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
E	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time <u>during the past 4 weeks</u>…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!