ANGIOX® (BIVALIRUDIN)
PROTOCOL NO. TMC-BIV-08-03

E.U.R.O.M.A.X
EUROpean aMbulance Acs angioX trial

EudraCT Nr. 2008-007290-20
Drug Development Phase: IIIb
Version: FINAL
Date: 16 April 2010
Amendment date: 24 April 2012
Sponsor: The Medicines Company UK Ltd.
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This study will be conducted in compliance with Good Clinical Practice (GCP) and protection of the patient as required by the regulations and directives in operation at this time.
## CONTACT DETAILS IN CASE OF EMERGENCY

<table>
<thead>
<tr>
<th>Role in Study</th>
<th>Name</th>
<th>Telephone number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Information (24 hour)</td>
<td></td>
<td>00 800-843-63-326 or +41-61-564-1320</td>
</tr>
<tr>
<td>Clinical Study Leader</td>
<td>Diana Schuette</td>
<td>+44 7970 942 022</td>
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<tr>
<td>Responsible Physician</td>
<td>Efthymios Deliargyris</td>
<td>+49 89244180876</td>
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1. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>The Medicines Company</th>
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<tr>
<td>Name of Investigational Product:</td>
<td>Bivalirudin (Angiox®)</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Bivalirudin</td>
</tr>
<tr>
<td>Title of Study:</td>
<td>European Ambulance Acute Coronary Syndrome Angiox Trial: EUROMAX</td>
</tr>
<tr>
<td>Study centre(s):</td>
<td>Approximately 50 centres located in Europe.</td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>Ph. Gabriel Steg</td>
</tr>
<tr>
<td>Investigators:</td>
<td>Christian Hamm, Patrick Goldstein, Martial Hamon, Lutz Nibbe, Arnoud van t’Hof, Peter Clemmensen, Uwe Zeymer, Jennifer Adgey</td>
</tr>
<tr>
<td>Study period (years):</td>
<td>Actual date first patient enrolled: 10 March 2010</td>
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<td>Estimated date last patient completed: May 2014</td>
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<tr>
<td>Objectives:</td>
<td>To show that the early administration of bivalirudin improves 30 day outcomes when compared to the current standard of care in patients with ST segment elevation acute coronary syndrome (STE-ACS), intended for a primary percutaneous coronary intervention (PCI) management strategy, presenting either via ambulance or to centres where PCI is not performed.</td>
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<tr>
<td>Methodology:</td>
<td>Multi-centre, multi-national, prospective, randomised, open-label, comparison of bivalirudin to other guideline based current therapies (excluding bivalirudin).</td>
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<tr>
<td>Number of patients (planned):</td>
<td>Approximately 2200</td>
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<tr>
<td>Diagnosis and main criteria for inclusion:</td>
<td>High risk adult patients (≥18 years), presenting either via ambulance or to centres where PCI is not performed with an onset of symptoms of &gt;20 minutes and &lt;12 hours, will be enrolled based on a diagnosis of:</td>
</tr>
<tr>
<td></td>
<td>• STE-ACS planned for a primary PCI management strategy with ST segment elevation of ≥1 mm in ≥2 contiguous leads, or presumably new left bundle branch block, or an infero-lateral myocardial infarction (MI) with ST segment depression of ≥1 mm in ≥2 of leads V1-3 with a positive terminal T wave.</td>
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<td></td>
<td>To be included in the study all patients should receive as soon as logistically feasible a European Society of Cardiology (ESC) guideline recommended dose of:</td>
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<td></td>
<td>• Aspirin at an initial dose of 150-325 mg orally (or 250-500 mg IV) followed by 75-100 mg/day for at least 1 year.</td>
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<td></td>
<td>• A loading dose of an approved P2Y₁₂ receptor blocker such as clopidogrel, prasugrel or ticagrelor that should be continued as per ESC guidelines (preferably for one year) in all patients.</td>
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<tr>
<td>All patients must be scheduled for angiography +/- PCI (if indicated) &lt;2 hours after first medical contact.</td>
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<td>Enrolment of patients will be stratified based on centre.</td>
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<tr>
<td>Investigational product, dosage and mode of administration:</td>
<td>• Bivalirudin: given immediately upon enrolment as bolus of 0.75 mg/kg followed immediately</td>
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by an infusion of 1.75 mg/kg/h. This infusion should be run continuously until completion of PCI at which time the infusion should be reduced to a dose of 0.25 mg/kg/h for at least 4 hours. An optional higher-dose infusion of 1.75 mg/kg/h is also permitted for up to 4 hours.

Patients who do not undergo PCI and are to be medically managed may continue the infusion of 0.25 mg/kg/h for up to 72 hours.

Patients who are to undergo coronary artery bypass grafting (CABG) are to undergo anticoagulation as per local practice. Post-PCI anticoagulation for prophylaxis or otherwise may be continued as per the local practice.

Reference therapy, dosage and mode of administration:

- **Control:** Any guideline-driven standard of care as outlined in the European Society of Cardiology Dosing Guidelines for Management of STE-ACS (Appendix 03) not including bivalirudin: Unfractionated heparin (UFH) (100 IU/kg with no glycoprotein IIb/IIIa inhibitor (GPI) and 60 IU/kg with a GPI); +/- routine or bail out eptifibatide (two 180 µg/kg boluses with a 10 minute interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours) or tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18 to 24 hours) or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours (maximum dose, 10 µg/min) [Zeymer, 2007; Goodman et al, 2008; van t’Hof et al, 2008].

Patients who are to undergo CABG are to undergo anticoagulation as per local practice. Post PCI anticoagulation for prophylaxis or otherwise may be continued as per the local practice.

**Primary Endpoint at 30 days:**

- A composite of death and non-CABG-related protocol major bleeding

**Secondary Endpoints:**

- Death or re-infarction (MI) at 30 days
- Death at 30 days and 365 days
- Re-infarction (MI) at 30 days
- IDR at 30 days
- Death, re-infarction (MI) or IDR at 30 days
- Death, re-infarction (MI) or non-CABG-related protocol major bleeding at 30 days
- Major bleeding at 30 days (protocol, TIMI and GUSTO)
- Minor bleeding at 30 days (protocol, TIMI, and GUSTO)
- Incidence of thrombocytopenia post index procedure and at 30 days
- Stent thrombosis (ARC definition) at 30 days
- Stroke at 30 days

**Sub-Analysis:**

- ST segment resolution sub-analysis (Appendix 04)

**Sample Size:** The sample size was determined based on the comparison of the composite primary endpoint of death and non-CABG-related protocol major bleeding at 30 days between patients in the bivalirudin and standard of care arm therapies for the trial population. We assume the event rates in patients with STE-ACS to be 4.25% in the bivalirudin arm versus 7.0% in the control arm. The sample size will provide 80% power at two sided alpha level of 0.05 for the primary comparison of death and major bleeding at 30 days.
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<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ARC</td>
<td>Academic Research Consortium</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Grafts</td>
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<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
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<tr>
<td>CK-MB</td>
<td>Creatine Kinase MB Isoenzyme</td>
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<td>CPK</td>
<td>Creatine Phosphokinase</td>
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<td>CRO</td>
<td>Clinical Research Organisation</td>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>dL</td>
<td>Decilitre(s)</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>FMC</td>
<td>First Medical Contact</td>
</tr>
<tr>
<td>GUSTO</td>
<td>Global Utilisation of Streptokinase and tPA for Occluded Coronary Arteries</td>
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<tr>
<td>GPI</td>
<td>Glycoprotein IIb/IIIa Inhibitor</td>
</tr>
<tr>
<td>h</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals</td>
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<tr>
<td>IDR</td>
<td>Ischaemia Driven Revascularisation</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>Institutional Review Board</td>
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<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
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<td>IV</td>
<td>Intravenous</td>
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<td>IVRS</td>
<td>Interactive Voice Response System</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>kg</td>
<td>Kilogram(s)</td>
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<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
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<tr>
<td>MACE</td>
<td>Major Adverse Cardiovascular Events</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram(s)</td>
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<td>MITT</td>
<td>Modified Intent-to-treat Population</td>
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<tr>
<td>mL</td>
<td>Millilitre(s)</td>
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<tr>
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</tr>
<tr>
<td>min</td>
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<td>NSTEMI</td>
<td>Non-ST-Segment Elevation Myocardial Infarction</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>Non-ST-Segment Elevation Acute Coronary Syndrome</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
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<td>Serious Adverse Event</td>
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<td>STEMI</td>
<td>ST-Segment Elevation Myocardial Infarction</td>
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<td>STE-ACS</td>
<td>ST-Segment Elevation Acute Coronary Syndrome</td>
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<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
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<tr>
<td>UA</td>
<td>Unstable Angina</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated Heparin</td>
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<tr>
<td>WPW</td>
<td>Wolff Parkinson White Syndrome</td>
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<td>y</td>
<td>Year(s)</td>
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4. INTRODUCTION

This protocol describes a study to compare bivalirudin to current therapies in patients (≥18 years) with STE-ACS (for >20 minutes and <12 hours) presenting either via ambulance or to centres where PCI is not performed, that are intended for a primary PCI management strategy. This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

4.1. Background

Randomised trials have established that patients presenting with STE-ACS should be ideally managed with primary PCI where feasible. Rapid diagnosis of the clinical syndrome, initiation of aggressive anti-thrombotic treatments based on a foundation of aspirin, clopidogrel and unfractionated heparin, transfer to the catheter laboratory for angiography and then definitive treatment directed by the anatomical findings may currently be regarded as the standard of care across Europe [Van de Werf et al, 2008].

Anticoagulants are used in the treatment of STE-ACS to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events [Goodman et al, 2008; Harrington et al, 2008]. There is clear evidence that anticoagulation is effective in addition to platelet inhibition and that the combination of the two is more effective than either treatment alone [Patrino et al, 2008].

The outcomes associated with pre-hospital administration of heparin, fibrinolytics and glycoprotein IIb/IIIa inhibitors have been previously investigated [Liam et al, 2000; Zijlstra et al, 2002; ASSENT-4 PCI Investigators, 2006; Ellis et al, 2008; van t’Hof et al, 2008]. Bivalirudin has not yet been evaluated in the setting of upstream anti-thrombotic therapy initiated in an ambulance bridging to invasive management of STE-ACS. Furthermore, a prolonged post-PCI infusion of bivalirudin may further reduce peri-procedural ischaemic complications in high risk patients [Stone et al, 2008].

4.2. Bivalirudin

Bivalirudin is currently indicated in the EU for “the treatment of adult patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention and as an intravenous (IV) anticoagulant in patients undergoing percutaneous coronary intervention (PCI) including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Bivalirudin is intended for use with aspirin and clopidogrel.”

Synthesised chemically, bivalirudin is a short peptide of 20 amino acids that binds to both the active site and substrate recognition exosite of thrombin, thus, directly and specifically inhibiting all known actions of thrombin [Leger et al, 2006]. These include protease actions such as conversion of fibrinogen to fibrin and direct cellular signalling actions such as activation of platelets [Coughlin, 1999; Kahn et al, 1999; Coughlin, 2000; Leger et al, 2006]. Unlike heparins (unfractionated or low molecular weight), bivalirudin inhibits both fluid phase and fibrin bound thrombin with similar potency – providing a distinct pharmacological advantage particularly in ACS patients. Furthermore, heparins potentiate platelet activation, whereas bivalirudin inhibits
platelet aggregation by blocking thrombin signalling to the protease activated receptor (PAR) family of platelet receptors – which are the most potent switches for platelet activation [Xiao and Theroux, 1998; Anand, 1999; Aggarwal et al, 2002; Keating et al, 2005; Keating et al, 2006; Schneider et al, 2006]. The effects of bivalirudin on thrombin are reversible – thrombin recognises the drug as a substrate and cleaves the active-site binding moiety resulting in reduced affinity and displacement of the remaining portion of the molecule by fibrinogen or other thrombin substrates. The plasma half-life of bivalirudin is 25 minutes. Complete reviews of preclinical safety and pharmacology studies are provided in the Investigator’s Brochure, provided with this protocol.

4.2.1. Preclinical studies

An overview of preclinical studies is given in the Investigator’s Brochure.

4.2.2. Clinical studies

HORIZONS AMI was a prospective, randomised, open label, double arm, single blinded trial in STEMI patients undergoing primary PCI [Stone et al, 2008]. Eligible patients were randomised in a 1:1 trial fashion to receive either bivalirudin monotherapy with a provisional GPI or UFH plus a routine GPI. After angiography, patients were triaged to primary PCI, CABG, or medical management, with the majority undergoing primary PCI. For patients triaged to primary PCI, a second randomisation occurred in a 1:3 fashion to a bare metal stent or a paclitaxel drug eluting stent.

Patients were included in the study if they were age 18 years or older, had symptoms of STEMI lasting for at least 20 minutes and occurring within the past 12 hours (including ST segment elevation of ≥1 mm in ≥2 contiguous leads, or presumably new left bundle branch block, or true posterior MI with ST segment depression of ≥1 mm in ≥2 contiguous anterior leads), and included patients with cardiogenic shock, and left main disease.

A total of 3,602 patients were randomised in the HORIZONS AMI trial at 123 sites in 11 countries between March 25, 2005 and May 7, 2007. At 30-days, bivalirudin monotherapy demonstrated statistical superiority versus UFH plus GPI for the two primary endpoints of net adverse clinical outcomes (9.2% versus 12.1% p=0.006) and major bleeding (4.9% versus 8.3% p=0.0001), and no significant differences for the secondary endpoint of major adverse cardiovascular events (5.4% versus 5.5% p=0.95).

When large haematomas were excluded from the protocol definition of major bleeding, bivalirudin reduced major bleeding from 7.8% with heparin plus a GPI to 4.7% (P=0.0001). In addition to reducing the 30-day rates of major bleeding as defined by the protocol, bivalirudin compared to heparin plus a GPI reduced haemorrhagic complications as defined by the TIMI and GUSTO scales, thrombocytopenia, and the need for blood product transfusions. Treatment with bivalirudin rather than heparin plus a GPI also resulted in significantly lower 30-day rates of cardiac mortality (1.8% versus 2.9%, RR[95%CI] = 0.62 [0.40, 0.95], P=0.028) and all-cause mortality (2.1% versus 3.1%, RR[95%CI] = 0.66 [0.44, 1.00], P=0.047), with non significantly different rates of re-infarction, target vessel revascularization, and stroke.

A recent published substudy from HORIZONS AMI further emphasized the importance of in-hospital non CABG-related major bleeding as a powerful predictor of long term mortality out to 3 years of follow-up. Specifically, the impact of major bleeding on mortality was observed.
within 30 days (HR 6.22, p<0.001), between 30 days and 1 year (HR 6.00, p<0.001) and between 1 year and 3 years (HR 3.67, p<0.001) [Suh JW et al, 2011].

Among 3,124 patients in whom stents were successfully implanted, the overall rate of stent thrombosis at 30 days was not significantly different in the bivalirudin and heparin plus GPI arms (2.5% versus 1.9%, P=0.30). However, within the first 24 hours, stent thrombosis developed in 17 more patients assigned to bivalirudin alone than heparin plus a GPI (1.3% versus 0.3%, P<0.001), whereas between 24 hours and 30 days, stent thrombosis occurred in 7 fewer patients in the bivalirudin group (1.2% versus 1.7%, P=0.28). Among the acute stent thrombosis patients, there were 2 deaths, 1 of which occurred in the bivalirudin alone group, and 1 in the heparin plus GPI group. Among the sub-acute stent thrombosis patients, there were 17 deaths, 3 of which occurred in the bivalirudin group, and 14 in the heparin plus GPI group.

4.2.3. Known and potential risks and benefits

Potential risks and benefits of bivalirudin are included in the investigator’s brochure.

4.3. Study Rationale

Current ESC guidelines for the treatment of STE-ACS recommend a primary PCI strategy be undertaken for patients who can achieve a first medical contact to balloon time of <120 minutes [Van de Werf et al, 2008].

In support of these aggressive reperfusion strategies the question of a facilitated approach with the administration of the first anti-thrombin(s) in the pre-hospital setting is of increasing interest. However, the range and choice of anti-thrombin medications available to clinicians is increasing and there remains some confusion over the optimal anti-thrombotic regimen [Goodman et al, 2008; Harrington et al, 2008; Patrono et al, 2008]. Furthermore, the addition of P2Y12 antagonists and GPI to augment platelet inhibition has increased the risk of bleeding, costs and complexity of treatment. The optimal regimen would be characterised by the (1) lowest incidence of ischaemic complications, (2) lowest incidence of bleeding complications and (3) most practical and cost-effective treatment.

In the HORIZONS-AMI trial [Stone et al, 2008] there was an increase in early ischaemic events in patients treated with bivalirudin. Based on the short half life of bivalirudin (25 minutes) and a strategy of discontinuing the infusion at the end of the procedure, in combination with the fact that maximum platelet inhibition after the pre-procedural dose of clopidogrel takes approximately 2 hours (if a 600 mg bolus used) [von Beckerath et al, 2005], bivalirudin treated patients may have been exposed to a period with little or no anti-thrombin treatment with ongoing post-procedural platelet activation.

As a direct thrombin inhibitor which suppresses thrombin mediated platelet activation, bivalirudin has the potential to improve current treatment strategies by replacing heparin and GPI [Stone et al, 2006; Stone et al, 2007a; Stone et al, 2007b; Stone et al, 2008]. Based on the potentially synergistic effects of bivalirudin and P2Y12 receptor blockade when used in combination [Andre et al, 2003; Nylander et al, 2004], a 600 mg loading dose of clopidogrel (or alternatively prasugrel) administered at enrolment (or as soon as logistically feasible) is likely to provide the most rapid and effective P2Y12 blockade in a high risk group of patients undergoing primary PCI [von Beckerath et al, 2005; Montalescot et al, 2009]. Additionally, continuing the
infusion of bivalirudin for 4 hours after the PCI will provide ongoing anti-thrombotic protection until such time as P2Y\textsubscript{12} inhibition has taken maximal effect.

A bivalirudin based anti-thrombotic strategy initiated in a pre-hospital setting and continued for 4 hours post PCI in combination with a P2Y\textsubscript{12} receptor blocker, such as clopidogrel, may in comparison to conventional strategies: (1) demonstrate similar protection against ischaemic events, (2) show a reduction in major and minor bleeding events, (3) obviate the need for the use of GPI, (4) reduce the risk of peri-procedural stent thrombosis, and; (5) simplify treatment and reduce costs.

4.4. **Study Population**

The study population will comprise men and non-pregnant women with STE-ACS, presenting either via ambulance or to centres where PCI is not performed, that are intended for a primary PCI management strategy. Patients will provide written informed consent.
5. **TRIAL OBJECTIVES AND PURPOSE**

The purpose of the trial is to show that the early administration of bivalirudin improves 30 day outcomes when compared to the current standard of care in patients with STE-ACS, with an onset of symptoms of >20 minutes and <12 hours, intended for a primary PCI management strategy, presenting either via ambulance or to centres where PCI is not performed.

All patients are to receive treatment with aspirin orally (150-325 mg or 250-500 mg IV) followed by 75-100 mg/day for at least 1 year and an approved P2Y\textsubscript{12} receptor blocker (such as clopidogrel, prasugrel or ticagrelor) as soon as logistically feasible and to be continued as per ESC guidelines (preferably for one year) in all patients. The primary objectives of the trial are to show that, when compared with standard anti-thrombotic therapies other than bivalirudin (which includes treatment with unfractionated heparin and optional GPI) that at 30 days:

- Bivalirudin is superior to control at reducing a composite of death and non-CABG-related protocol major bleeding.
6. TRIAL DESIGN

6.1. Stratification

To ensure appropriate distribution of variables that may affect the primary endpoint, the primary randomisation will be stratified based on:

- The enrolling centre

6.2. Primary Endpoint

The primary endpoint of this trial at 30 days is:

- A composite of death, and non-CABG-related protocol major bleeding

6.3. Secondary Endpoints

- Death or re-infarction (MI) at 30 days
- Death at 30 days and 365 days
- Re-infarction (MI) at 30 days
- IDR at 30 days
- Death, re-infarction (MI) or IDR at 30 days
- Death, re-infarction (MI) or non-CABG-related protocol major bleeding at 30 days
- Major bleeding at 30 days (protocol, TIMI and GUSTO)
- Minor bleeding at 30 days (protocol, TIMI, and GUSTO)
- Incidence of thrombocytopenia post index procedure and at 30 days
- Stent thrombosis (ARC definition) within 30 days
- Stroke at 30 days

6.4. Trial Endpoint Definitions

**Death:** will be defined as death from any cause at any time during the study period and for up to 1 year following randomisation. In addition, the cause of death (cardiac versus non-cardiac) will be captured. Cardiac death is defined as death due to any of the following:

- Acute myocardial infarction
- Heart failure
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- Cerebrovascular accident suspected of being related to the index procedure (PCI/CABG)
- Death due to complication of the index procedure (PCI/CABG)
• Any death in which a cardiac cause cannot be excluded

Non-cardiac death is defined as a death not due to cardiac causes (as defined above), including bleeding-related death.

**All Bleeding events:** will be characterised as related or unrelated to surgery (CABG).

**Protocol Major Bleeding:** will be characterised as unrelated to surgery (CABG) and defined as any one of the following:

- Intracranial
- Retroperitoneal
- Intraocular
- Access site haemorrhage requiring radiological or surgical intervention
- Reduction in haemoglobin concentration of $>4g/dL$ (2.5 mmol/L) without an overt source of bleeding
- Reduction in haemoglobin concentration of $>3g/dL$ (1.8 mmol/L) with an overt source of bleeding
- Re-intervention for bleeding
- Use of any blood product transfusion

**Protocol Minor Bleeding:** will be defined as all other observed non-CABG-related bleeding or transfusion events.

**TIMI Major Bleeding** is defined as [Bovil et al, 1991]:

- Intracranial haemorrhage
- Associated with a decrease in Hgb $>5g/dL$ (3.1 mmol/L) (or 15% of haematocrit)
- Haemorrhagic Death
- Cardiac Tamponade

**TIMI Minor Bleeding** is defined as [Bovil et al, 1991]:

- Blood loss that is spontaneous and observed as gross haematuria or haematemesis
- Observed (ie, haeme-positive coffee ground emesis, haeme-positive melaena, haematoma or retroperitoneal bleeding)
- Spontaneous or non-spontaneous blood loss associated with a haemoglobin $>3$ g/dL (1.8 mmol/L) and $<5$ g/dL (3.1 mmol/L) (or a haematocrit decrease of 9% and $<15\%$)
- Haemoglobin decrease $>4$ g/dL (2.5 mmol/L) and $<5$ g/dL (3.1 mmol/L) (or 12% of haematocrit and $<15\%$) with, despite attempts, no bleeding site identified

**GUSTO Severe or life-threatening** is defined as [GUSTO Investigators, 1993]:

- Either intracranial haemorrhage or bleeding that causes hemodynamic compromise and requires intervention
GUSTO Moderate is defined as [GUSTO Investigators, 1993]:

- Bleeding that requires blood transfusion but does not result in hemodynamic compromise

GUSTO Mild is defined as [GUSTO Investigators, 1993]:

- Bleeding that does not meet criteria for either severe or moderate bleeding

Re-infarction (MI):

The occurrence of re-infarction (MI) will be assessed up to the 30 day time point. **Serial ECGs, and biomarkers should be obtained for each suspected recurrent ischaemic event.** A positive diagnosis of re-infarction (NEW event) not associated with index PCI is made when the following criteria are met:

<table>
<thead>
<tr>
<th>Subsequent Ischaemic Events</th>
<th>Subsequent Ischaemic Events</th>
<th>Subsequent Ischaemic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;24 hours</strong></td>
<td><strong>24 hours to 7 days</strong></td>
<td><strong>&gt;7 days</strong></td>
</tr>
</tbody>
</table>
| Symptoms such as chest pain, lasting ≥20 minutes, presumed to be ischaemic in origin. (a) | Symptoms such as chest pain, lasting ≥20 minutes, presumed to be ischaemic in origin. (a) | The “Universal definition” of MI

Myocardial infarction should be determined based evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

1. 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 ischaemia with at least one of the following:
   - Symptoms of ischaemia;
   - ECG changes indicative of new ischaemia (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.

2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary 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.

3. For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognised.

4. For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.

5. Pathological findings of an acute myocardial infarction.
(a) In the absence of pain, new ST segment changes indicative of ischaemia, acute pulmonary oedema, ventricular arrhythmias, or hemodynamic instability presumed to be ischaemic in origin, will constitute sufficient evidence of ischaemia.

(b) New Q waves are defined as Q waves with a duration of >0.04 seconds in at least 2 contiguous leads that were not present on previous ECGs. These ECG criteria are only valid in the absence of left bundle branch block (LBBB), Wolff Parkinson White syndrome (WPW), paced rhythm or other artefacts that would preclude an ECG definition of myocardial infarction.

(c) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in the presence of biomarker elevation with or without other defining factors of myocardial infarction (clinical, ECG, biochemical) and in the absence of a non-ischaemic cause may also be used to define a re-infarction. A wall motion abnormality alone does not define infarction.

Criteria for Prior Myocardial Infarction
Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause. (c)
- Pathological findings of a healed or healing myocardial infarction. (c)

Q-wave versus Non Q-wave infarction
All re-infarctions will be classified as being either Q-wave (development of new pathological Q-waves with a duration of >0.04 seconds in at least 2 contiguous leads that were not present on previous ECGs) or non Q-wave.

Ischaemic Driven Revascularisation (IDR): IDR is defined as any refractory ischaemia-driven repeat percutaneous intervention or bypass graft surgery involving any native coronary or pre-existing bypass graft vessel. In the absence of pain, new ST segment changes indicative of ischaemia, acute pulmonary oedema, ventricular arrhythmias, or haemodynamic instability presumed to be ischaemic in origin, will constitute sufficient evidence of ischaemia. The episode of ischaemia leading to repeat PCI or CABG must occur following completion of the index procedure.

Stent thrombosis: Based on the ARC definition, stent thrombosis can be defined as Definite, Probable and Possible Stent thrombosis [Cutlip et al. 2007]:

Definite stent thrombosis
- Angiographic confirmation of stent thrombosis
  - The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
    - Acute onset of ischemic symptoms at rest
    - New ischemic ECG changes that suggest acute ischemia
    - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
  - Nonocclusive thrombus
    - Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence
of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

- Occlusive thrombus
  - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).
- Pathological confirmation of stent thrombosis
  - Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

**Probable stent thrombosis:**
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

**Possible Stent Thrombosis:**
For subjects with intracoronary stenting prior to randomization, clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after last known intracoronary stenting up to and including the 30 day study time point.

Stent Thrombosis can be:

- **Acute:** (within 24 hours post-index PCI)
- **Sub-acute:** (>24 hours and ≤30 days post-index PCI)
- **Late:** (>30 days post-index PCI)

In the absence of stent implantation, the same definitions may be applied to define “vessel thrombosis.”

**Thrombocytopenia:** will be defined as a post-procedural platelet count <100,000 cells/mm³ in a patient with a baseline or pre-procedural platelet count >100,000 cells/mm³. Further divided into mild (50,000 - <100,000 cells/mm³), moderate (20,000 - <50,000 cells/mm³), or severe (<20,000 cells/mm³, or requiring platelet transfusion).

**Stroke:** is defined as a sudden, focal neurological defect resulting from a cerebrovascular cause, resulting in death or lasting greater than 24 hours, that is not due to a readily identifiable cause such as a tumor, infection or trauma.

All suspected strokes will be adjudicated using all available clinically relevant information including imaging studies to classify all strokes as:

- Haemorrhagic stroke – a stroke with focal collections of intracranial blood
- Ischaemic stroke – a stroke without focal collections of intracranial blood
- Unknown – no imaging or autopsy data are available
ST Segment Resolution Sub-Analysis: This sub-analysis will examine the hypothesis that routine pre-hospital bivalirudin is non-inferior to routine pre-hospital UFH and GPI with regard to the extent of myocardial reperfusion (ST segment resolution) in patients with STE-ACS, intended for treatment with primary PCI. The data collection and analyses are specified in Appendix 04.

6.5. Type/Design of Trial

This is a multi-centre, multi-national, prospective, randomised, open-label comparison of bivalirudin to current therapies. Approximately 2200 patients will be randomised. Informed consent will be obtained from patients meeting the inclusion criteria before the initiation of any study specific procedures. Immediately following informed consent, administration of the study medications will commence as described below.
6.6. **Schematic Diagram of Trial Design**

![Diagram](image)

6.7. **Measures to Minimise/Avoid Bias**

The trial is open-label. Randomisation will occur by the use of randomisation envelopes. Despite the obvious benefits of a double-blind design, the logistics of a double-blind approach to the evaluation of bolus UFH, bolus and infusion bivalirudin, and provisional administration of pre-hospital or catheter laboratory GPI are not feasible and are potentially limiting in a large international trial with pre-hospital and hospital phases. Furthermore, all efforts must be taken not to retard time to reperfusion in patients with STE-ACS.

An independent Clinical Events Committee (CEC) will adjudicate all primary clinical endpoints plus stroke and stent thrombosis. The committee members and the CEC management team will be completely blinded to the randomised therapy, as well as any patient identifying information. The CEC will adjudicate the events based on pre-determined definitions outlined in Section 6.4. Other measures to avoid or minimise bias introduced by the open-label design will include intent-to-treat principles of analysis and use of objective measures for repeat myocardial infarction, ischaemia driven revascularisation and bleeding endpoints.

6.8. **Randomisation**

Patients that satisfy the entry criteria for the study and having provided written informed consent will be randomised via the randomisation envelope method in order to minimise bias based on patient selection and baseline characteristics. The primary randomisation is to one of two anti-thrombotic regimens in a 1:1 ratio stratified by site.
All patients with STE-ACS are to undergo a primary PCI based management strategy with angiography within <2 hours of first medical contact with a view to PCI, +/- CABG or medical management (as indicated). Regardless of triage to PCI, CABG or medical management all patients will remain in the ITT population and complete follow up at 30-days and mortality at 1 year.
7. **SUBJECT POPULATION**

7.1. **Number of Subjects**

Approximately 2200 patients will be studied at approximately 50 centres located in Europe.

7.2. **Inclusion Criteria**

The decision to randomise patients must be made by a qualified physician or paramedic who is present at the time.

Subjects may be included in the study if they present either via ambulance or to a centre where PCI is not performed and meet all of the following criteria:

1. Provide written informed consent before initiation of any study related procedures. Patients randomised in the ambulance may initially sign an abridged version.
2. Be aged ≥18 years at the time of randomisation.
3. Have a presumed diagnosis of a STE-ACS with onset of symptoms of >20 minutes and <12 hours with one or more of the following:
   - ST segment elevation of ≥1 mm in ≥2 contiguous leads
   - Presumably new left bundle branch block
   - An infero-lateral MI with ST segment depression of ≥1 mm in ≥2 of leads V1-3) with a positive terminal T wave
4. All patients must be scheduled for angiography +/- PCI (if indicated) <2 hours after first medical contact

7.3. **Exclusion Criteria**

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomisation:

1. Any bleeding diathesis or severe haematological disease or history of intra-cerebral mass, aneurysm, arterio-venous malformation, haemorrhagic stroke, intra-cranial haemorrhage or gastrointestinal or genitourinary bleeding within the last 2-weeks.
2. Patients who have undergone recent surgery (including biopsy) within the last two weeks.
3. Patients on warfarin (not applicable if INR known to be <1.5).
4. Patients who have received UFH, LMWH or bivalirudin immediately before randomisation.
5. Thrombolytic therapy within the last 48 hours.
6. Absolute contraindications or allergy that cannot be pre-medicated to iodinated contrast or to any of the study medications including aspirin or clopidogrel.

7. Contraindications to angiography, including but not limited to severe peripheral vascular disease.

8. If it is known pregnant or nursing mothers. Women of child-bearing age will be asked if they are pregnant or think that they may be pregnant.

9. If it is known a creatinine clearance <30 mL/min or dialysis dependent.

10. Previous enrolment in this study.

11. Treatment with other investigational drugs or devices within the 30 days preceding randomisation or planned use of other investigational drugs or devices in this trial.

12. Patients may not be enrolled if the duration of randomised investigational medicinal product (IMP) anti-thrombin infusion is likely to be less than 30 minutes from the time of onset to the commencement of angiography.

13. Patients may not be enrolled within a primary PCI capable hospital (unless at the time of randomisation the catheter laboratory is not available and the patient requires transfer to another primary PCI capable hospital).


7.4. Withdrawal Criteria

All patients have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue any patient at any time if medically necessary. It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

- adverse event(s), including an event resulting in death
- abnormal laboratory value(s)
- abnormal test procedure result(s)
- unsatisfactory therapeutic effect
- protocol violation
- patient withdrew consent
- lost to follow-up
- administrative reasons

It is imperative to obtain complete follow-up data for all patients whether or not they receive their assigned treatment or have discontinued study drug. Every attempt should be made to collect follow-up information except for those patients who specifically withdraw consent to release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the Study Drug should be carried out
when possible whether or not a patient continues to receive treatment according the protocol. Patients will not be replaced in this trial.
8. TREATMENT OF SUBJECTS

8.1. Study Medications

To be included in the study all patients should receive as soon as logistically feasible an ESC guideline recommended dose of:

- Aspirin at an initial dose of 150-325 mg orally (or 250-500 mg IV) followed by 75-100 mg/day orally for at least 1 year.
- A loading dose of an approved P2Y₁₂ receptor blocker such as clopidogrel, prasugrel or ticagrelor that should be continued as per ESC guidelines, preferably for one year in all patients.

It is recommended to re-administer aspirin and a P2Y₁₂ receptor blocker to patients on chronic pre-randomisation therapy.

For patients randomised to:

- **Control:** Any guideline-driven standard of care as outlined in Appendix 03 not including bivalirudin: UFH (100 IU/kg with no GPI and 60 IU/kg with a GPI); +/- routine or bail out eptifibatide (two 180 µg /kg boluses with a 10 minute interval followed by an infusion of 2.0 µg /kg/min for 72-96 hours) or tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18 to 24 hours) or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours (maximum dose, 10 µg/min) [Zeymer, 2007; Goodman et al, 2008; van t’Hof, 2008].
- **Bivalirudin:** given immediately upon enrolment as bolus of 0.75 mg/kg followed immediately by an infusion of 1.75 mg/kg/h. This infusion should be run continuously until completion of PCI at which time the infusion should be reduced to a dose of 0.25 mg/kg/h for at least 4 hours. An optional higher-dose infusion of 1.75 mg/kg/h is also permitted for up to 4 hours. Patients who do not undergo PCI and are to be medically managed with continuing anticoagulation should continue the bivalirudin infusion of 0.25 mg/kg/h for up to 72 hours.

Once a patient has commenced treatment with an anti-thrombin (with the exception of Fondaparinux) no change in strategy is recommended.

Routine post-PCI anticoagulation is prohibited. In patients requiring ongoing anticoagulation for specific indications other than PCI (eg, DVT prophylaxis, haemofiltration, atrial fibrillation or intra-aortic balloon pump), then anti-coagulation should be maintained as per local practice.

**Glycoprotein IIb/IIIa Inhibitor Management:** In patients randomised to the control arm the use of a GPI will be classified as either “routine” (treatment of patients before or during angiography but not once PCI has commenced) or “bail out” (treatment of patients during or after PCI).
Patients randomised to bivalirudin may only have a “bail out” GPI (abciximab bolus + 12 hour infusion or eptifibatide double bolus + 12-18 hour infusion or tirofiban bolus followed by an 18 to 24 hour infusion) administered during primary PCI for the following two reasons only:

- The presence of a “giant” thrombus adjacent to the stent or in the coronary vessel (length >2x that of the diameter of the coronary vessel) after PCI in the absence of a mechanical obstruction
- Sustained no reflow (TIMI 0-1 flow in the absence of a mechanical obstruction, refractory to intracoronary nitrates, adenosine or a calcium channel blocker delivered intracoronary to the distal coronary bed via an infusion catheter)

**Renal Impairment:** As indicated, any of the above drug doses are to be adjusted for renal impairment according to their respective Summary of Product Characteristics.

**CABG:** Patients who are to undergo CABG are to undergo anticoagulation as per local practice.

**Prohibited Concomitant Medications**

1. Patients on warfarin (not applicable if INR known to be <1.5).
2. Thrombolytics within 48 hours, as per the exclusion criteria
3. Routine post-PCI anticoagulation is prohibited. In patients requiring ongoing anticoagulation for specific indications other than PCI (eg, DVT prophylaxis, haemofiltration, atrial fibrillation or intra-aortic balloon pump), then anti-coagulation should be maintained as per local practice.

**Treatment Compliance**

The treatment, dosage and period of administration for each study medication given must be documented. A monitor will review a selection of patient source documents and drug accountability records to assess treatment compliance on an ongoing basis during site visits.

### 8.2. Study Drug

See the *Pharmacy Manual* for complete details and requirements for study drug packaging, labelling, storage, preparation, administration and accountability.

### 8.3. Study Drug Packaging and Labelling

Bivalirudin will be provided by the Sponsor as open-label stock. Commercial hospital stock supplies of bivalirudin are not permitted to be used for this trial.

Bivalirudin will be provided in kits of two (2) open-label vials per box. Refer to the Pharmacy Manual for more details.

Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

Aspirin, unfractionated heparin and GPI will be obtained from hospital stock and prepared as per standard practice as outlined in the Appendix 3 and Section 8.1.
8.4. **Study Drug Storage**
Bivalirudin will be stored in a securely locked cabinet at the appropriate conditions as specified in the Pharmacy Manual. Access should be strictly limited to the investigators and their designees. Neither the investigators nor any designees may provide investigational bivalirudin to any subject not participating in this protocol.

8.5. **Study Drug Preparation**

8.5.1. **Bivalirudin**

- **Vial Reconstitution**
  Reconstitute each 250 mg vial with 5 mL of preservative free sterile water for injection to yield a clear opalescent, colourless to slightly yellow solution, pH 5.0-6.0, with a concentration of 50 mg/mL. Gently swirl until all material is dissolved (1-2 minutes). Do not shake. The reconstituted vial (50 mg/mL) is stable at 2-8°C for up to 24 hours.

- **Syringe Driver/Bag Preparation**
  The contents of one reconstituted vial, 5 mL (250 mg) should then be added to a 50 mL of 0.9% sodium chloride for injection or 5% dextrose in water. The prepared infusion will yield a final concentration of approximately 5 mg/mL. If it is known that the duration of therapy will be lengthy or that the patient will be receiving the high infusion rate, it is permissible to make larger volumes, however the concentration should remain at 5 mg/mL, regardless of the volume prepared.

8.6. **Administration**
Refer to protocol Section (8.1) and/or the *Pharmacy Manual* for specifics on study drug administration.

8.7. **Study Drug Accountability**
The investigator or his designee must maintain an inventory record of bivalirudin received and all administered to assure the regulatory authorities and the Sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

The bivalirudin supplied for use in this study is to be prescribed only by the Principal Investigator (PI) or named sub-investigators and may not be used for any purpose other than that outlined in this protocol.

8.8. **Study Drug Handling and Disposal**
At the termination of the study, all unused bivalirudin will be destroyed on site as permitted by local regulations. In the event that bivalirudin needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.
8.9. **Sequence of Procedures**

The Schedule of Events summarises the study assessments by time point.

This study consists of 3 periods:

**The Pre-Hospital Phase:** consists of confirming eligibility, randomisation, and refers to collection of data regarding treatments administered in the ambulance or non-primary PCI capable referring hospital.

**The In-Hospital Phase:** refers to the collection of data from arrival in the PCI capable hospital until discharge home or 7-days (whichever comes first), including any period of in-patient care occurring post-PCI back in a referring hospital.

**The Follow-Up Phase:** consists of data collection at 30 days (± 5 days) post randomisation by an out-patient follow up visit and mortality at 1 year (± 30 days) post randomisation either by a follow-up telephone call or by viewing a centralised death register (if available).
## Table 1: Visit Schedule

<table>
<thead>
<tr>
<th>STE-ACS</th>
<th>PRE-HOSPITAL</th>
<th>IN-HOSPITAL</th>
<th>FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Management</td>
<td>Pre-Catheter Laboratory</td>
</tr>
<tr>
<td>History and examination (Killip class)</td>
<td>X</td>
<td>X (9)</td>
<td>X</td>
</tr>
<tr>
<td>Review inclusion exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG (12-lead)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Informed consent (8)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (1)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor blocker (2)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer of bivalirudin or control (5)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology &amp; chemistry (6)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogram within 120 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-infarction (MI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major &amp; minor bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AE assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE assessment (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Confidential FINAL 24 April 2012; Amendment 2
(1) Aspirin at an initial dose of 150-325 mg orally (or 250-500 mg IV) followed by 75-100 mg/day for at least 1 year.

(2) A loading dose of an approved P2Y₁₂ receptor blocker such as clopidogrel, prasugrel or ticagrelor that should be continued as per ESC guidelines (preferably for one year) in all patients.

(3) If randomised to bivalirudin following PCI, the reduced infusion dose of 0.25 mg/kg/h is resumed for 4 hours. An optional higher-dose infusion of 1.75 mg/kg/h is also permitted for up to 4 hours. If randomised to heparin no IV heparin infusion should be started routinely either during or after the procedure. In patients requiring ongoing anti-coagulation for reasons other than PCI (eg, haemofiltration, atrial fibrillation or intra-aortic balloon pump) then anti-coagulation should be maintained as per local practice.

(4) SAEs only to be collected at 30 days. SAEs will be assessed and recorded on the eCRF from randomisation up until to 30 days after study drug cessation and reported in accordance with Clinical Trial Directive guidance ENTR/CT 3.

(5) Bivalirudin or control (any ESC guideline based standard of care)

(6) Haematology consisting of haemoglobin (Hgb), haematocrit (Hct), platelets (total and corrected), chemistry consisting of creatinine collected on the screening sample only.

(7) Non-serious AEs will be assessed and recorded on the eCRF from randomisation up until hospital discharge or Day 7, whichever comes first following cessation of study drug infusion, regardless of causal relationship to the study drug.

(8) Due to the nature of this study, it will not be possible to present the patients that are randomised in an ambulance with the complete patient information sheet. Thus for patients presenting in the ambulance, an abridged version of the patient information sheet will be read out to the patient by qualified medical, nursing or paramedical staff. The staff will then sign the consent form to confirm that study information was read to the patient and the patient will also be asked to sign the form. Should the patient be unable to provide signature, retrospective consent will be sought when reasonably practical. Once it is reasonably practical, the full version of the patient information sheet will be given to the patient for information. For patients presenting to investigational sites not capable of PCI, consent will be obtained prior to any study procedures (including any pre-treatment procedures) are performed.

(9) History and Killip class only collected once after arrival in hospital at pre-catheter laboratory time point.
8.10. **General Conduct of the Trial**

Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all patients before the performance of any protocol-specific procedures.

8.11. **Pre-Hospital Screening**

The subject must meet the inclusion/exclusion criteria before the randomisation centre is contacted for treatment assignment.

The following procedures will be performed:

- Review of inclusion and exclusion criteria
- Explanation of the study to the subject with a date and signature documented on an informed consent document
- AE/SAE reporting commences
- 12-lead ECG
- Blood haematology (haemoglobin, haematocrit, platelets [total and corrected])
- Blood chemistry (creatinine)
- Biomarkers (preferably Troponin I or Troponin T or alternatively CK-MB (mass) or CPK)

8.12. **Pre-Hospital Management**

Immediate management following randomisation comprises:

- Endpoint reporting (death, major & minor bleeding, stroke and thrombocytopenia) commences and AE/SAE reporting continues
- History and examination (Killip class)
- Aspirin at an initial dose of 150-325 mg orally (or 250-500 mg IV)
- A loading dose of an approved P2Y₁₂ receptor blocker such as clopidogrel, prasugrel or ticagrelor
- Collection of concomitant medication
- Initiation of either bivalirudin or control *as soon as logistically feasible* post-randomisation

8.13. **In-Hospital Management**

*Immediate management in the pre-catheter and catheter laboratory comprises:*

- Endpoint reporting (death, major & minor bleeding, stroke and thrombocytopenia) and AE/SAE reporting continues
- Continue infusion of bivalirudin if randomised to treatment with bivalirudin
• 12-lead ECG
• Collection of concomitant medication
• Angiography within 120 minutes of first medical contact (FMC)

**In-hospital management post-index procedure:**

• Endpoint reporting of re-infarction (MI), IDR and stent thrombosis commences and all other endpoint reporting and AE/SAE reporting continues
• If randomised to bivalirudin following PCI, the reduced infusion dose of 0.25 mg/kg/h is resumed for at least 4 hours. An optional higher-dose infusion of 1.75 mg/kg/h is also permitted for up to 4 hours
• If randomised to heparin no IV heparin infusion should be started routinely either during or after the procedure
• In patients requiring ongoing anti-coagulation for reasons other than PCI (eg, haemofiltration, atrial fibrillation or intra-aortic balloon pump) then anti-coagulation should be maintained as per local practice
• 12-lead ECG (1 hour +/- 30 minutes), and at day 7 or discharge. *Additional ECGs should only be obtained for a suspected recurrent (NEW) ischaemic event.*
• Examination (blood pressure and heart rate)
• Collection of concomitant medication
• Blood haematology (haemoglobin, haematocrit, platelets [total and corrected]) daily for at least 2 days and on day 7 or discharge
• Blood chemistry (creatinine) daily for at least 2 days and on day 7 or discharge
• Biomarkers (24 hours +/- 1 hour) and 48 hours (+/- 1 hour) (preferably Troponin I or Troponin T or alternatively CK-MB (mass) or CPK)) *should only be obtained for a suspected recurrent (NEW) ischaemic event*
• Aspirin continued at 75-100 mg/day for at least 1 year
• An approved P2Y12 receptor blocker (such as clopidogrel, prasugrel or ticagrelor) should be continued as per ESC guidelines (preferably for 1 year) in all patients in whom PCI was performed

**Management of Subsequent Ischaemic Events:** Serial ECGs and biomarkers should be obtained for each suspected recurrent ischaemic event.

**Suspected Re-Occlusion:** The patient who initially had chest pain relief with improvement in the ECG who later develops prolonged chest pain with new ischaemic ECG changes (suspected re-occlusion) should undergo emergency repeat catheterisation. Further treatment is per operator discretion based on the angiographic findings. Anticoagulation regimens per local standard practice should be used.
8.14. Follow-up Management

Clinical follow-up (visit to a local hospital or general practitioner) will take place at 30 days (± 5 days) in all patients undergoing randomisation. Original source documents must be collected for any clinical events. Should the patient be re-admitted to a non-study hospital, all possible efforts should be made to obtain original source documents from that hospital.

On discharge, for all patients in whom a PCI was performed, aspirin (75-100 mg/day) and a daily therapy of an approved P2Y₁₂ receptor blocker (such as clopidogrel, prasugrel or ticagrelor) should be continued as per ESC guidelines, preferably for one year.

30-Day Follow-up Period

All subjects will require a follow-up visit (to a local hospital or general practitioner) at 30 days (± 5 days) after randomisation. Subjects will undergo screening of SAEs, concomitant medication, ECG, blood haematology and chemistry. They will also be questioned regarding any hospitalisations for episodes of ischaemia (re-infarction (MI), IDR, stent thrombosis) and bleeding (protocol major and minor bleeding or thrombocytopenia) that may have occurred in the period between the index hospitalisation and the 30 day time point. If it is ascertained that the subject has died, the date and cause of death should be recorded on the eCRF.

1-Year Follow-up Period

The 1 year follow-up for death will be conducted either by telephone call or by viewing a centralised death register (if available). If it is ascertained that the subject has died, the date and cause of death should be recorded on the eCRF.
9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse event

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

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the subject was randomised in a clinical study are not to be considered AEs.

The severity of an AE and the relationship to study drug will be assessed by the investigator. The investigator should ensure that any patient experiencing an AE receives appropriate medical support until the event resolves.

9.1.2. Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (It does not include an event that, had it occurred in a more severe form, might have caused death),
- results in persistent or significant disability/incapacity,
- requires hospitalisation or prolongs hospitalisation,
- results in a congenital anomaly/birth defect, or
- is another medically significant event that, based upon appropriate medical judgment, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a re-infarction (MI) that may be considered minor could also be an SAE if it prolonged hospitalisation.
Study Endpoints

In accordance with ENTR/CT 3 endpoints (non-CABG-related protocol major bleeding, re-infarction (MI), thrombocytopenia, stroke, stent thrombosis and ischaemia driven revascularisation) and symptoms of endpoints as defined in Section 6.4 will be collected in the eCRF to support the assessment of endpoints and should not be reported as AE unless fatal. However, all deaths occurring within 30 days following the study drug cessation must be reported as SAEs, regardless of underlying cause and relationship to study drug.

9.2. Procedure for Adverse Event Recording

All AEs (non-serious and serious) must be recorded on the source documents and eCRFs provided by the Sponsor.

Non-serious AEs will be assessed and recorded on the eCRF from randomisation up until hospital discharge or day 7, whichever comes first following cessation of study drug infusion, regardless of causal relationship to the study drug. SAEs will be assessed and recorded on the eCRF from randomisation up until to 30 (±5 days) days after study drug cessation and reported in accordance with Clinical Trial Directive guidance ENTR/CT 3.

9.3. Procedure for Serious Adverse Event Reporting

In addition to entering each SAE, irrespective of causality, on the appropriate AE page of the eCRF, the investigator must complete a Serious Adverse Event Report (SAER) for each SAE regardless of causality to study drug, occurring from randomisation up to 30 days after study drug cessation. The SAER must be submitted to the Drug Safety Designee, Sentrx within 24 hours from the point in time when the site first becomes aware of the SAE. Sentrx or The Medicines Company will contact the investigator should it be necessary to clarify any of the event information. The investigator should provide any follow-up information for the event to Sentrx as soon as it becomes available and up to the point the event has been resolved.

This reporting requirement is applicable to SAEs that occur during the designated study period. If the investigator is notified of a SAE after the study that he or she determines to be causally related to study drug, the event should be reported through the process described above.

9.4. Procedure for Endpoint Reporting

All endpoints (not serious and serious) spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded. All endpoints (both related and not related to study drug) must be recorded on the source documents and eCRFs provided by the Sponsor. Events meeting the definition of an endpoint (re-infarction, major and minor bleeding, IDR, and stent thrombosis) will not be reported as SAEs unless the event is fatal. All deaths, regardless of underlying cause and relationship to study drug, will be reported as SAEs if they occur up to and including 30 days of study drug cessation.
10. PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee should contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject’s continuation in the study. The EC will be informed of all protocol changes by the investigator in accordance with the EC established procedure.
11. STATISTICAL PLAN

11.1. Sample Size

The sample size was determined based on the comparison of the composite primary endpoint of death and non-CABG-related protocol major bleeding at 30 days between patients in the bivalirudin and standard of care arm therapies for the trial population. We assume the event rates in patients with STE-ACS to be 4.25% in the bivalirudin arm versus 7.0% in the control arm. The sample size will provide 80% power at two sided alpha level of 0.05 for the primary comparison of death and non-CABG-related protocol major bleeding at 30 days.

11.2. Definitions

11.2.1. Subject populations

For this trial, the following populations will be defined and used in the analysis and/or presentation of the data.

**Intent-to-treat (ITT) population:** The ITT population will be defined as all subjects randomised into the trial. Treatment classification will be based on the randomised treatment.

**Per-protocol (PP) population:** The PP population will be defined as all subjects randomised into the trial who received their randomised treatment and who underwent angiography.

**Safety population:** The safety population will be defined as all randomised subjects who received study drug, and will be classified according to the actual treatment received.

The primary and secondary efficacy analyses will be based on the ITT population. Analyses based on the PP populations will be considered secondary and confirmatory. All safety analyses will be performed on the safety population.

11.2.2. Observational period

The observational period for the study will be 365 (±30) days. Any event occurring after the defined observational period, even if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the patient data listings.

11.3. Statistical Analysis

Continuous variables will be summarised by means, standard deviations (SD), medians, inter-quartile ranges and minimum and maximum values. Categorical variables will be summarised by frequencies and percentages.

11.4. Primary Endpoint

The primary endpoint is the composite incidence of death and non-CABG-related protocol major bleeding evaluated at 30 days (±5 days) using the ITT population. A subject is defined to have a composite event if the subject experiences at least 1 of the 2 components (death or non-CABG-related protocol major bleeding) of the composite.
The primary analysis will be based on the event rate of the composite endpoint of death or non-CABG-related protocol major bleeding and tested using a 2-sided binomial test of proportions with $\alpha=0.05$. The primary null hypothesis is that there is no difference between the bivalirudin arm and the standard of care arm. The sample size provides at least 80% power for the test of this hypothesis.

11.5. Secondary Endpoint(s)

- Death or re-infarction (MI) at 30 days
- Death at 30 days and 365 days
- Re-infarction (MI) at 30 days
- IDR at 30 days
- Death, re-infarction (MI) or IDR at 30 days
- Death, re-infarction (MI) or non-CABG-related protocol major bleeding at 30 days
- Major bleeding at 30 days (protocol, TIMI and GUSTO)
- Minor bleeding at 30 days (protocol, TIMI, and GUSTO)
- Incidence of thrombocytopenia post index procedure and at 30 days
- Stent thrombosis (ARC definition) at 30 days
- Stroke at 30 days

The above-defined secondary endpoints will be analysed in a manner similar to the primary endpoint. No multiple comparison adjustments will be applied to the secondary endpoint analyses.

The ST segment resolution analysis is detailed further in Appendix 04.

11.6. Interim Analysis

The interim analysis will be based on the primary composite of death or non-CABG-related protocol major bleeding at 30 days after randomisation in the ITT population. Interim analyses will be conducted by the DSMB and will include the following:

- Group sequential tests will be performed using the Peto boundary [Peto et al, 1976].

Table 2: Peto Boundary

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Upper Boundary</th>
<th>Nominal Alpha</th>
<th>Cumulative Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>3.09023</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>100%</td>
<td>1.97737</td>
<td>0.024</td>
<td>0.025</td>
</tr>
</tbody>
</table>
Since the primary objective is to show superiority of bivalirudin over the standard of care, the lower boundary is of little interest and the upper boundary will be considered to be a 1-sided, 2.5% boundary.

- Sample size re-estimation will also be performed following the enrolment of 70% of patients and the sample size may be increased if necessary. In the case of the decision for a sample size increase, the inclusion criteria may be broadened in order to ensure rapid enrolment and timely study completion. The test statistic for the final analysis may be adjusted, using the algorithm suggested by Gao, Ware and Mehta (2008) [Gao et al, 2008].

Additional interim analyses will be performed periodically by the DSMB as needed to monitor safety.

11.7. Procedure for Amendments to Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that due to the study observations, some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.

11.8. Data Collection

An electronic Case Report Form (eCRF) will be used to collect all patient data assessments that will be used for evaluation of specified analyses.

11.9. Accountability

The investigator or his designee must maintain an inventory record of bivalirudin received and all administered to assure the regulatory authorities and the Sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

The bivalirudin supplied for use in this study is to be prescribed only by the Principal Investigator or named sub-investigators and may not be used for any purpose other than that outlined in this protocol.

At the end of the study, all unused bivalirudin will be destroyed locally once the bivalirudin has been accounted for and the monitor has reviewed the accountability records. In the event that bivalirudin needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.
12. RECORDS RETENTION

Current EU Directive and ICH guidelines collectively require that essential clinical trial documents (including case report forms) other than the subject’s medical files must be retained for the following time period:

- For at least 15 years after completion or discontinuation of the trial,
- Or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region,
- Or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Investigators shall retain the essential documents relating to a clinical trial for at least five years after its completion. They shall retain the documents for a longer period, where so required by applicable local requirements.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records.
13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfil these obligations, the Sponsor will authorise a Clinical research Organisation (CRO) or independent contractors to perform monitoring tasks and visit the centre(s) during the study in accordance with the Clinical Management Plan (CMP) set forth for this trial as well as maintain frequent telephone and written communication. The investigator will permit the Sponsor’ authorised CRO personnel to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol is adhered to.

13.2. Auditing

As part of implementing quality assurance, the Sponsor may conduct audits at the study centre(s) in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP and applicable regulatory requirements. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. Regulatory authorities worldwide may inspect the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with regulatory authority inspections as required.
14. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, with the Sponsor’s standard operating procedures and/or guidelines, European Union regulations, the International Conference on Harmonisation (ICH) GCP guidelines and the Declaration of Helsinki.

The investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol and GCP requirements. Also, each investigator must complete and sign the Investigator's Agreement. In signing, the investigator agrees to:

- Adhere to the Investigator Agreement
- Participate in Investigator meetings as scheduled by the Sponsor
- Maintain up-to-date angiographic and PCI equipment
- Have access to cardiac surgery
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply angiographic material suitable for quantitative analysis
- Obtain written Informed Consent from each study participant before any study specific procedures are performed in accordance with GCP
- Complete all electronic CRFs for completed patients visits and or applicable events (i.e., death, re-infarction (MI), IDR, non-CABG-related protocol major bleeding) prior to scheduled monitoring visits
- Adhere to the study protocol at all times, except to eliminate an immediate hazard to trial subject(s). Comply with all European Union requirements for investigators, and with all other applicable regulations and codes of approvals from ECs and other Regulatory Authorities.

14.1. Informed Consent

The investigator(s) has both ethical and legal responsibility to ensure that each prospective subject is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same EC responsible for approval of this protocol.

Due to the nature of this study, it will not be possible to present patients that are randomised in an ambulance with the complete patient information sheet. Thus for patients presenting in the ambulance, an abridged version of the patient information sheet will be read out to the patient by qualified medical, nursing or paramedical staff. The staff will then sign the consent form to confirm that study information was read to the patient and the patient will also be asked to sign the form. Once it is reasonably practical, the full version of the patient information sheet will be given to the patient for information. Should the patient be unable to provide signature,
retrospective consent will be sought when reasonably practical. This process may however vary from country to country. Guidance will be sought on the consenting process from the local authorities. For patients presenting to investigational sites not capable of PCI, consent will be obtained prior to any study procedures (including any pre-treatment procedures) are performed (full consent).

Each patient shall be given a copy of the signed informed consent form, and the original shall be kept in the site’s regulatory file. A second copy may be filed in the patient's medical record, if allowed by the institution.

14.2. Ethics Committee

This protocol and the written informed consent form shall be submitted to the appropriate EC in each European country. The study may not commence until written approval from the EC is available, either as a letter or as a copy of the appropriate section of the EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an EC member, the written approval must indicate such non-participation. The Sponsor or authorised designee will submit status reports to the EC at least annually (when applicable and according to local regulations). The EC must be notified by the Sponsor or designee in writing of the interruption and/or completion of the study; the Sponsor or designee must promptly report to the EC all changes in research (protocol amendments) and will not make such changes without EC approval except where necessary to eliminate apparent immediate hazards to human patients. In these cases, the EC must be notified within five days of the change. The Sponsor or designee will promptly report to the EC all unanticipated problems involving risk to patients or others. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the EC and must agree to share all such documents and reports with the Sponsor or designee.
15. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorised regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and patient bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only initials and unique patient numbers in CRFs will identify patients. In countries where patient initials may not be used the unique patient number will be the only identifier. Patients full names may, however, be made known to a product regulatory agency or other authorised official if necessary.

16. PUBLICATION POLICY

The sponsor of this study, recognising the seminal importance of this investigation, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. At the conclusion of the EUROMAX Trial, a multi-centre abstract reporting the primary results will be prepared by the Principal Investigator (in collaboration with the Executive Committee, International Steering Committee, Publication Committee and local principal investigators from high enrolling sites) and presented at an annual high calibre scientific meeting. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single centre experience within the trial is not allowed until both the preparation and publication of the multicenter results. Following analysis and presentation of the primary endpoint results, active participation of all committee members and investigators from high enrolling sites, will be enthusiastically solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the study Principal Investigator after review by the Sponsor and Executive Committee.

All original manuscripts and abstracts of data and information relating to the clinical trial described in this protocol (collectively, “Publications”) will be submitted in advance to the Publication Committee for review according to the procedure described in this section. The Publication Committee will act as an independent body of scientific and medical experts with the following charter:

- The Publication Committee must review and approve all proposed analyses and topics suggested by the investigators and participating institutions in the clinical trial;
- All Publications discussing the trial data and conclusions must be submitted to the Publication Committee for review and approval prior to submission for presentation or publication; and
- All other Publications relating to the clinical trial will be submitted to the Publication Committee for review and comment prior to submission for presentation or publication.
All draft Publications must be submitted to the Publication Committee at least 30 days prior to submission to a journal or public presentation. The Publication Committee will consider each manuscript proposal with due regard for the scientific merit of the proposed publication. Decisions of the Publication Committee will be by majority vote. All manuscripts approved by the Publication Committee will conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.
17. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Investigator’s Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the investigational drug [bivalirudin], the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Ethics Committee (EC) responsible for such matters in the Clinical Study Facility where bivalirudin will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this EC approved protocol will be submitted to the European Medicines Agency (EMEA) and other regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilised by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records at the research facility for patients screened or randomised in the study.

I agree to provide all patients with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, and ICH guideline, Part E6, Section 4.11.

______________________________________________
Principal Investigator

______________________________________________
Date
18. REFERENCES


Keating FK, Dauerman HL, Whitaker DA, Sobel BE, Schneider DJ. The effects of bivalirudin compared with those of unfractionated heparin plus eptifibatide on inflammation and thrombin generation and activity during coronary intervention. Coron Artery Dis 2005 Sep;16(6):401-5.


Zeymer U. Eptifibatide versus Abciximab in Primary PCI for Acute ST Elevation Myocardial Infarction; Scientific Sessions of the AHA, Late Breaking Clinical Trials, Orlando, Florida. 2007.

APPENDIX 01 - SEVERITY AND CAUSALITY ASSESSMENTS FOR ADVERSE EVENTS

SEVERITY

Adverse events (AEs) will be graded on a 3-point scale and reported as indicated on the electronic case report form. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.
2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe: Inability to work or perform normal daily activity.

STUDY DRUG CAUSALITY

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

• temporal relationship to the initiation of study medication
• response of the event to withdrawal of study medication
• AE profile of concomitant therapies
• clinical circumstances during which the AE occurred
• patient’s clinical condition and medical history

Categorisation* of causality will be designated by the investigator as stated below:

1. Unrelated - this category applies to AEs that are clearly due to causes other than the study medication.
2. Unlikely related - this category applies to AEs for which there is no reasonable evidence or argument to suggest a causal relationship between the study medication and the AE.
3. Possibly related - this category applies to AEs for which there is reasonable evidence or argument to suggest a causal relationship between the AE and the study medication.
4. Definitely related - this category applies to AEs that are considered to be related to the study medication, with a high degree of certainty.

* for the purposes of regulatory reporting, categories ‘3’ and ‘4’ will be considered “related”.

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APPENDIX 02 - STUDY COMMITTEES

The Sponsor will appoint chairmen and members to the Executive Committee, the International Steering Committee and to an independent DSMB.

Executive Committee
This committee will be composed of physicians considered expert in the field of Emergency Medicine, ACS and PCI, including a physician from the Sponsor. The members will provide the scientific direction for the trial. In consultation with the DSMB, this group will be responsible for evaluating the progress of the trial and will make recommendations to the Sponsor regarding termination or continuation thereof. Further, this committee, in collaboration with the Sponsor, may decide to increase or decrease the sample size.

Clinical Events Committee (CEC)
A CEC will be formed to review clinical data and to adjudicated all primary endpoints plus stroke and stent thrombosis while blinded to the assigned study drug. The CEC will be composed of physicians. The CEC processes will be described in the CEC charter.

International Steering Committee
This committee will be composed of physicians considered experts in the field of Emergency Medicine, ACS and PCI. As a rule, each participating country will have at least one representative of emergency physicians and one representative of hospital cardiologists. The members will provide the scientific direction for the trial, with particular focus on national and regional variations in practice that may differ across Europe.

Data and Safety Monitoring Board (DSMB)
An independent DSMB will monitor the progress of the trial and ensure that the safety of subjects enrolled in the trial is not compromised. The DSMB will consist of a clinical chairman, several physicians experienced in clinical trials, but not participating in this study and at least 1 statistician. The DSMB processes is described in the DSMB charter.

Publications Committee
The Publication Committee will be comprised of a minimum of 5 physician representatives of institutions participating in the study and 1 physician from the Sponsor. The members will be appointed by the Executive Committee. The Publication Committee will be co-chaired by the physician from the Sponsor and 1 physician representative.
APPENDIX 03 – EUROPEAN SOCIETY OF CARDIOLOGY DOSING GUIDELINES FOR MANAGEMENT OF STE-ACS*

Relief of pain, breathlessness and anxiety

- IV opioids (4 to 8 mg morphine) with additional doses of 2 mg at 5 to 15 minute intervals
- O₂ (2–4 L/min) if breathlessness or other signs of heart failure
- Tranquilliser - in very anxious patients

Doses of anti-platelet concomitant therapies with primary PCI

- Aspirin: oral dose of 150-325 mg or IV dose of 250-500 mg if oral ingestion is not possible
- Clopidogrel: oral loading dose of at least 300 mg preferably 600 mg
- Abciximab: IV bolus of 0.25 mg/kg bolus followed by 0.125 μg/kg per minute infusion (maximum 10 μg/min for 12 hours)

Doses of anti-thrombin concomitant therapies with primary PCI

- Heparin: IV bolus at a usual starting dose of 100 U/Kg weight (60 U/kg if GPI is used).

If the procedure is being performed under activated clotting time (ACT) guidance, heparin is given at a dose able to maintain an ACT of 250 to 350s (200-250s if GPI are used).

*Reference: [Van de Werf et al, 2008].
APPENDIX 04 – ST SEGMENT RESOLUTION SUB-ANALYSIS

Sub-analysis Investigators
Dr. Arnoud van t’Hof
Dr. Peter Clemmensen
Dr. Uwe Zeymer
Dr. Christian Hamm

Sub-Analysis Rationale

Current ESC and AHA guidelines for the treatment of STE-ACS recommend a primary PCI strategy be undertaken for patients who can achieve a first medical contact to balloon time of <120 minutes. The EUROMAX study will investigate administration of pre-hospital bivalirudin versus the European standard of care which may or may not include the routine administration of pre-hospital GPI. There is evidence that the routine administration of pre-hospital GPI may improve outcomes when compared to catheter laboratory administration of GPI [Ortolani et al, 2008; van’t Hof et al, 2008; Huber et al, 2007; De Luca, 2008]. As a direct thrombin inhibitor which suppresses thrombin mediated platelet activation, routine pre-hospital administration of bivalirudin has the potential to improve current treatment strategies by replacing heparin (unfractionated or low molecular weight), and GPI antagonists.

This sub-study hypothesizes that routine pre-hospital bivalirudin is non-inferior to routine pre-hospital UFH and GPI with regard to the extent of myocardial reperfusion (ST segment resolution) in patients with STE-ACS, intended for treatment with primary PCI.

Myocardial Reperfusion (ST segment resolution or residual ST segment deviation)

The extent of myocardial reperfusion can be assessed using electrocardiographic parameters (ST segment resolution or residual ST segment deviation). The evaluation of ST segment resolution has been shown to be a reliable method to analyse myocardial perfusion and infarct size in patients with STEMI treated by pharmacological or mechanical reperfusion. In fact, early resolution of ST segment elevation correlates with myocardial salvage after reperfusion therapy [Schröder R et al, 1994, Dong et al, 2002]. It was previously reported that in patients with post-procedural TIMI 3 flow, ST segment resolution added significant prognostic information with respect to long-term mortality [van’t Hof et al, 1997]. Results of more recent studies indicate that ST segment resolution predicts both short- and long-term outcomes for patients who have undergone PCI. In a post hoc analysis of the CADILLAC study maximum residual ST segment deviation post PCI of <1 mm was present in 59% patients after PCI (despite restoration of TIMI flow grade 3 in 96% of patients) [McLaughlin et al, 2004]. By this measure, reperfusion is suboptimal in 41% after PCI. ST segment resolution therefore, may reflect myocardial flow rather than epicardial flow and predict clinical outcome better than epicardial vessel patency alone [Brodie et al, 2005]. The mechanism is probably related to the extent of microvascular injury. A large area of myocardium at risk or an ischaemic time of more than 3 hours results in
oxidative stress and a lack of recovery of aerobic metabolism, subsequent micro circulation plugging of capillaries, oedema and further impediment of flow.

**Primary Hypothesis**

Early pre-hospital initiation of bivalirudin is **non-inferior** to early pre-hospital initiation of a GPI inhibitor with regard to the residual ST segment deviation in millimeters 1 hour **after** angiography or PCI in patients with ST segment elevation myocardial infarction.

**Methodology**

ECG analyses will be performed by an independent blinded ECG core laboratory. Measurements will be made by two readers blinded to clinical and angiographic data and the time of ECG recording as well as the randomisation scheduled. ECG’s will be done upon randomisation (screening ECG), upon arrival in the catheter laboratory (pre-catheter laboratory ECG) and 1 hour after PCI (1 hour post index procedure ECG). Patients with right bundle-branch block who clearly have ST segment elevation are included in the analysis. For patients not undergoing PCI post-angiography, a 12-lead ECG will also be performed 1 hour post-procedure. The absolute level of the ST segment deviation will be measured by digital calliper to the nearest 0.01 mv, 20 ms after the end of the QRS interval using the TP segment as iso-electric baseline [Schröder K et al, 2001]. Residual cumulative ST segment deviation on the single post-procedure ECG will be used for the assessment of the primary endpoint [Buller CE et al, 2008]. In addition, ST segment deviation resolution from paired ECG’s (baseline and post-procedure ECGs) will be calculated. ST segment resolution will be computed by dividing the extent of ST segment deviation on the pre- or post-procedure ECG by the extent of ST segment deviation on the baseline (diagnostic) ECG. Patients will be divided into 3 groups of ST segment resolution: complete resolution, defined as >70% resolution, partial resolution, defined as >30% but <70% resolution and no resolution, defined as <30% resolution, as described previously [Schröder R et al, 1994, van’t Hof et al, 1997]. In addition, the extent of residual ST segment deviation on the single post-procedure ECG will be classified into 4 groups (0 mm = no residual ST segment deviation; 1-3 mm = residual ST segment deviation between 1 and 3 mm; 4-6 mm = residual ST segment deviation between 4 and 6 mm; >6 mm = residual ST segment deviation more than 6 mm), as described previously [De Luca et al, 2005].

**Primary End Point**

- Amount of residual ST segment deviation (millimeters) 1 hour post index-PCI (based on 1 hour post index procedure ECG).

**Secondary End Points**

- Incidence of complete ST segment resolution before angiography or PCI (based on pre-catheter laboratory ECG).
• Incidence of complete ST segment resolution 1 hour post-index PCI (based on 1 hour post index procedure ECG).

Patient Population

Analyses will be performed on the ITT population as defined in section 11.2. The population eligible for enrolment into the ST segment resolution sub-analysis will consist of patients who receive either pre-hospital bivalirudin or pre-hospital UFH and a GPI inhibitor. Treatment classification will be based on the randomised treatment.

Schematic Diagram of Sub-Analysis Design

Statistical Analyses

All ECG’s will be analysed including those ECG’s from patients who do not undergo angioplasty (candidates for CABG or conservative treatment). The residual ST segment deviation in millimeters (based on 1 hour post index procedure ECG) will be analysed using the t-test. And 95% confidence intervals for the mean residual ST segment deviation difference between the treatments will be presented. The primary non-inferiority (NI) null and alternative hypotheses are the following:

Null Hypothesis: \( X_b \geq X_c + \delta \)

Alternative Hypothesis: \( X_b < X_c + \delta \)

where,

\( X_b \) = Residual ST segment deviation 1 hr post index-PCI in the pre-hospital bivalirudin arm and 
\( X_c \) = Residual ST segment deviation 1 hr post index-PCI in the pre-hospital UFH and GPI (control) arm

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Delta ($\delta$) for NI = 1 mm difference.

A 1 mm NI margin was chosen because this difference in residual ST resolution deviation is clinically relevant. Since there are different recruiting centres, the primary endpoint results per centre will be examined to evaluate possible differences. An exploratory analysis across several pre-specified subgroups will also be performed.

The percentage of patients with complete ST segment resolution before angiography (based on pre-catheter laboratory ECG) and at 1 hour post PCI (based on 1 hour post index procedure ECG) will be analysed using the $\chi^2$ test or Fischer exact test.

In addition the $\chi^2$ test for trend will be used to analyse the percentages of patients in each of the four pre-specified groups of residual ST segment deviation (0 mm = no residual ST segment deviation; 1-3 mm = residual ST segment deviation between 1 and 3 mm; 4-6 mm = residual ST segment deviation between 4 and 6 mm; >6 mm = residual ST segment deviation more than 6 mm) and in each of the three groups of ST segment resolution (complete resolution, defined as >70% resolution, partial resolution, defined as >30% but <70% resolution and no resolution, defined as <30% resolution).

**Sample Size Calculation**

For this analysis the residual ST segment deviation (millimeters) 1 hour after PCI will be used (based on the 1 hour post index procedure ECG). The sample size calculation is based on the assumption that the mean residual ST segment deviation in the UFH + GPI arm will be $3.6 \text{ mm} \pm 4.6 \text{ mm}$. This expected mean ST segment deviation value is based on previous findings from the On-TIME 2 study [van’t Hof et al, 2008]. Based on this assumption, with 85% power to detect an absolute difference of up to 1 mm in the bivalirudin treated patients and a 2.5% significance level, 762 patients (381 from each randomised arm) are needed to show non-inferiority of pre-hospital bivalirudin to the standard treatment. To account for incomplete or un-interpretable ECG data in approximately 5% of patients, 800 patients should be included into this sub-analysis.
Reference List


