London, 29 August 2007
Product Name: **Arixtra**
EMEA/H/C/403/II/24

SCIENTIFIC DISCUSSION

I. SCIENTIFIC DISCUSSION

1.1. Introduction

The company is requesting the following new indication in the treatment of Acute Coronary Syndromes (ACS) for Arixtra 2.5 mg:
Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) ACS for the prevention of death, myocardial infarction and refractory ischaemia. Fondaparinux has been shown to reduce all cause mortality in patients with UA/NSTEMI.
Treatment of ST segment elevation myocardial infarction (STEMI) ACS for the prevention of death and myocardial re-infarction in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy. Fondaparinux has been shown to reduce all cause mortality in patients with STEMI.

As a consequence of the requested new indication, the MAH is also applying for major changes to sections 4.2 (posology) and 5.1 (Pharmacodynamic properties), and other changes in 4.3, 4.4, 4.8, 5.2 and section 6 of the SPC.

In order to treat the STEMI subset of ACS patients, the MAH is also applying for the approval of a new route of administration, namely intravenous, for the already existing 2.5 mg pre-filled syringe. This requested change is being processed through a separate Line Extension application (EMEA/H/C/403/X/25), and the details thereof will not be further discussed in this report.

The application is based on 2 large phase III pivotal studies (*OASIS 5* and *OASIS 6*) and 4 phase II supportive trials. These studies have investigated the efficacy and safety of fondaparinux in patients with ACS, with and without ST-segment elevation. No Scientific Advice was sought to discuss the design of the trials.

Rationale for the proposed change

The term acute coronary syndrome (ACS) includes UA, NSTEMI and STEMI, all of which share a common underlying pathophysiology. ACS normally results from the sudden rupture or erosion of an existing atheromatous plaque, which exposes a thrombogenic surface causing platelet activation and thrombus formation. The acute development of a coronary thrombus, in the case of UA/NSTEMI severely restricts, and in STEMI, completely occludes the culprit coronary artery, causing myocardial ischaemia and/or injury in the territory supplied by the affected vessel(s). Diagnostically on ECG, UA/NSTEMI typically results in depressed ST segments and/or T wave inversions, and STEMI produces elevated ST segments. The extent of any permanent myocardial damage is estimated by markers of cardiac injury (e.g. troponin, CPK MB) and is dependent on a number of factors such as duration of the ischaemia and the amount of myocardium supplied by the affected coronary artery.

ACS is a major cause of mortality and morbidity, and is a significant burden on health care resources. Each year there are at least 1.5 million hospitalisations for ACS in USA, with an estimated further 4 million worldwide. Over half are attributable to UA and NSTEMI and almost a third to STEMI. Not only is STEMI a significant public health burden in developed countries, but it is also becoming a major problem in developing countries. Registry data from developed countries suggests a shift towards declining incidence of STEMI and increasing incidence of UA, which may reflect detection earlier in the disease continuum, thus reducing the morbidity and mortality risk following patient presentation.

Patients with UA/NSTEMI exhibit a spectrum of risk for death and cardiac ischaemic events. Registry data reveals risk of in-hospital mortality rises for patients with a confirmed diagnosis of UA (1-3%), NSTEMI (5-6%) and STEMI (7-9%). These differences are also reflected in the 30-day mortality rates of 1.7%, 7.4% and 11.1%, respectively. Results from the GUSTO-11b trial also show a significantly higher 30-day mortality risk following STEMI compared to NSTEMI (6.1% vs 3.8% respectively). However, by the end of one year, the mortality risk did not differ significantly (9.6% vs 8.8%). In light of the high 1-year mortality rates, there remains a critical need for effective acute treatments in both

patient groups, despite the pharmacological options available. Furthermore, many of the currently available drugs are precluded in certain situations or populations, particularly where bleeding risk is a concern, or have significant drawbacks, such as the need for monitoring, the possibility of inducing HIT, and complex dosing regimens.

Currently available antithrombotic drugs are associated with an increased risk of bleeding. For example, the reported rates of major bleeding in GRACE were 4.7% and 4.8% for NSTEMI and STEMI patients, respectively. Recently it has been acknowledged that, in ACS patients, bleeding plays an important role in adverse outcome, including mortality. Moreover, a recent large registry study has shown that over 40% of ACS patients administered an antithrombotic agent (UFH, LMWH, or GPIIb/IIIa inhibitor) receive an incorrect dose. Overdosing was most prevalent in patient groups who were already at a high risk of bleeding, including the elderly, women and patients with renal impairment, and was associated with a higher risk of bleeding and increased mortality.

Thus, a major therapeutic advantage would be a drug with a simple dosing regimen, which is efficacious for the prevention of the sequelae of both UA/NSTEMI and STEMI, but which is not associated with an increased risk of bleeding. The anti-Factor Xa specificity of fondaparinux allows a more predictable anticoagulant response with no need for monitoring of coagulation parameters. In addition to being effective for the prevention of VTE in the venous circulation, fondaparinux was also expected to be an effective antithrombotic in the arterial circulation; due to its mechanism of action that ultimately inhibits the formation of thrombin. As already noted, thrombin inhibition is one of the mechanisms by which UFH and LMWH are believed to exert their beneficial effects in ACS patients.

1.2 Non-clinical aspects

Pharmacokinetic data indicate that fondaparinux was completely bioavailable in the rat and rabbit after subcutaneous administration, allowing extrapolation of SC data to IV data in terms of AUC. Previously submitted toxicological data sufficiently address the IV route and no additional data are considered necessary. Further details on the non-clinical aspects of the IV administration can be found in the AR of the concurrent line extension EMEA/H/C/403/X/25.

1.3 Clinical aspects

Overview of data submitted

The clinical development program for fondaparinux in ACS comprises 6 clinical studies; 4 were phase II studies (*PENTUA*, *PENTALYSE*, *ASPIRE* and *ACT 2445)* and 2 pivotal phase III studies (*OASIS-5* in UA/NSTEMI and *OASIS 6* in patients with STEMI), including a total of 34,071 subjects.

Study	Subject Population/No Subjects Randomised [1]	Treatment Groups	Fondaparinux Dose (once daily)	Treatment Duration
Phase II Studies				
PENTUA	UA/NSTEMI/1147	Fondaparinux vs Enoxaparin	2.5mg, 4mg, 8mg, 12mg s.c. after initial i.v. dose	3-7 days
PENTALYSE	STEMI/333	Fondaparinux vs UFH plus r-tPA in both arms	4mg, 8mg, 12mg s.c. after initial i.v. dose	4-6 days
ASPIRE	PCI/350	Fondaparinux vs UFH	2.5mg, 5mg i.v.	Single dose
ACT2445	PTCA/71/71	Fondaparinux	12mg i.v.	Single dose
Phase III Studies				
OASIS 5	UA/NSTEMI/20,078	Fondaparinux vs Enoxaparin	2.5mg s.c.	≤8 days
OASIS 6	STEMI/12,092	Fondaparinux vs standard care	2.5mg s.c. after initial i.v. dose	≤8 days

[1] 1147 subjects in *PENTUA* comprise 1138 who were randomised plus 9 treated subjects who were not randomised
UA unstable angina. NSTEMI non ST-elevation myocardial infarction. STEMI ST-elevation myocardial infarction PCI/PTCA percutaneous coronary intervention. UHF unfractionated heparin

The Clinical Study Reports state that all trials were conducted according to GCP.

Analysis of data submitted

Phase II studies

Four phase II studies included a total of 1,901 subjects and assessed a range of doses (2.5mg to 12mg) and dose regimens (IV and/or sc with single/repeat dosing) in a variety of clinical settings within the broad spectrum of ACS. Two were dose-ranging studies in subjects with UA/NSTEMI (PENTUA) and STEMI (PENTALYSE) that evaluated fondaparinux administered sc for up to 7 days following an initial iv dose. The other two phase II studies, ASPIRE and ACT2445 evaluated primarily the safety of iv bolus doses of fondaparinux administered as an adjunct during coronary interventions. ACT2445 assessed 12mg fondaparinux administered as an iv bolus prior to PTCA while the subsequent ASPIRE study provided reassurance that fondaparinux administered as either a 2.5 or 5.0mg iv bolus might be suitable as an adjunct to PCI in the phase III program. As the primary objective of these studies was a safety profile and not determination of the effective dose, they will not be detailed in this report.

PENTUA (63119):
A multicentre, double-blind, double-dummy, randomised, active-controlled, dose ranging study comparing four doses of fondaparinux (2.5mg, 4mg, 8mg and 12mg) and enoxaparin (1mg/kg BID) in subjects with UA or non-Q wave MI.

The primary *objective* was to assess the dose-response relationship of fondaparinux using a composite of death (any cause except bleeding), AMI or recurrent ischemia up to and including Day 9 as the primary endpoint, in order to select a suitable dose for future studies.

Diagnosis and Main Criteria for Inclusion: The study recruited hospitalised or non-hospitalised subjects with suspected or documented non-Q wave MI without persistent ST-segment elevation or with angina at rest or during minimal exertion and whose last episode of pain was <24 hours prior to the screening ECG with either dynamic ST segment changes or clear ST segment depression of ≥1mm and/or serum troponin T or troponin I concentrations >0.1ng/ml at screening. Subjects showing persistent ST segment elevation on the screening ECG compatible with an evolving AMI or subjects scheduled for PTCA or angiography within 24 hours or CABG within 48 hours of screening were excluded.

Doses of fondaparinux were 2.5mg, 4mg, 8mg or 12mg by SC injection OD after an initial IV bolus dose on Day 1 for a minimum of 3 and maximum of 7 days. The fondaparinux doses were adjusted for body weight; subjects weighing <50kg received 2mg, 3mg, 6mg or 9mg daily, whereas subjects weighing >100kg received 3mg, 5mg, 10mg or15mg daily. Subjects randomised to enoxaparin were treated with 1mg/kg BID by SC injection for a minimum of 3 and maximum of 7 days.

The *primary efficacy endpoint* was the composite of death from any cause (except bleeding), AMI and symptomatic recurrent ischemia up to and including Day 9. To support the primary efficacy analysis, the incidence of the composite endpoint was also assessed up to and including Day 30. The sample size calculation was based on the ability to detect a positive dose-response relationship and assumed an incidence of the composite endpoint of 50% in the lowest dose group and an incidence of 36% in the highest dose group. Assuming that approximately 10% of the enrolled subjects had major protocol violations, 1075 (215 per group) subjects had to be randomised in total. This sample size gave a power of 80% for the comparisons between each fondaparinux group versus enoxaparin, if the true difference between the groups was approximately 15%.

The primary safety analysis was on the incidence of major bleedings (overt bleeding associated with any of the following: death or life-threatening condition, operation to manage bleeding, retro-peritoneal, intracranial or in a critical organ, haemoglobin drop of >20g/l) from up to and including Day 9. The incidence of any bleeding (major or minor) was considered as a secondary safety endpoint.

Number of Subjects: In total, 1147 subjects were recruited at 64 centres in 5 countries. The intent-to-treat (ITT) population (all subjects randomised who received at least one dose of study drug) consisted of 1143 subjects. A total of 214 (18.7%) subjects had major protocol deviations resulting in a PP population for the primary efficacy analysis of 929 subjects (fondaparinux 2.5mg: 203 subjects; fondaparinux 4mg: 177 subjects; fondaparinux 8mg: 173 subjects; fondaparinux 12mg: 187 subjects; enoxaparin: 189 subjects).

Results:
There was no (linear) dose response relationship between the incidence of the primary endpoint and any of the tested fondaparinux doses. Indeed, the incidence of the primary efficacy endpoint was lowest in the fondaparinux 2.5mg group, whereas the incidence in the 4mg dose group was the highest (fondaparinux 2.5mg: 30.0%; fondaparinux 4mg: 43.5%; fondaparinux 8mg: 41.0%; fondaparinux 12mg: 34.8%; enoxaparin: 40.2%).
There was a significant reduction in the incidence of the composite primary endpoint at Day 9 in the fondaparinux 2.5mg group (30.0%) compared with the fondaparinux 4mg (43.5%, p=0.011), fondaparinux 8mg (41%, p=0.036) and the enoxaparin (40.2%, p=0.047) groups; all other differences were not statistically different. At Day 30 there was also a statistically significant reduction in the composite endpoint between the fondaparinux 2.5mg group (33.8%) and the fondaparinux 4mg group (44.9%, p=0.032). All other differences were not statistically different although the difference between the fondaparinux 2.5mg group (33.8%) and enoxaparin (43.6%) approached statistical significance (p=0.055).
There was no (linear) dose response relationship between the incidence of any bleeding event and any of the tested fondaparinux doses (fondaparinux 2.5mg: 3.9%; fondaparinux 4mg: 5.4%; fondaparinux 8mg: 5.4%; fondaparinux 12mg: 4.6%; enoxaparin: 4.8%). There were no statistically significant differences in the incidence of major bleeding up to Day 9 and up to Day 30 between the treatment groups.
In total there were 33 deaths, 23 deaths to Day 30 and 10 deaths after Day 30. The lowest incidence of death was found in the fondaparinux 2.5mg group (fondaparinux 2.5mg: 1.7%; fondaparinux 4mg: 4.5%; fondaparinux 8mg: 2.7%; fondaparinux 12mg: 2.9%; enoxaparin: 2.6%). Up to Day 90, the incidence of subjects with SAEs observed in the fondaparinux 2.5mg and enoxaparin group (7.9% and 7.4%, respectively) tended to be lower than in the other treatment groups (11.3%, 11.2% and 11.3% in the fondaparinux 4mg, 8mg and 12mg groups, respectively).

PENTALYSE:
A multicentre, open-label, randomised, active-controlled, parallel group, dose-ranging study comparing 3 doses of fondaparinux (4mg, 8mg and 12mg) and UFH as adjunctive therapy to recombinant tissue plasminogen activator and aspirin (ASA) in acute myocardial infarction (AMI).

The primary objective was to assess the safety and tolerability of 3 dose regimens of fondaparinux combined with recombinant rTPA and ASA in AMI. Secondary objectives included the assessment of the efficacy of the combination therapy for restoring and maintaining early coronary patency. The study recruited subjects with ischemic pain lasting at least 30 minutes, ST-segment elevation ≥0.1mV in two or more limb leads or ≥0.2mV in two or more contiguous precordial leads, for whom planned treatment was initiated within six hours of pain onset.
Treatment Administration: Subjects randomised to fondaparinux received a single IV bolus injection of fondaparinux 4mg, 8mg or 12mg on Day 1 followed by daily SC injections for 4±1 days. The daily dose was reduced by 2mg in the 8mg and 12mg groups for body weight <60kg and increased by 2mg in the 4mg and 8mg groups for body weight >90kg. Subjects randomised to UFH and weighing >67kg received an IV bolus of 5000IU on Day 1 followed by an IV infusion of 1000IU/h for 48-72 hours. For subjects weighing ≤67kg the dose of the IV bolus was 4000IU and the IV infusion was 800IU/h. The infusion rate was adjusted to maintain an activated partial thromboplastin time of 50 to 75 seconds.

The main efficacy endpoint was recovery of patency of the MI-related coronary artery (TIMI Grade 3 flow) 90 minutes after the start of thrombolytic therapy and on Day 6. Clinical endpoints of death,

reMI, emergency revascularisation procedure, and combined events during the 30±7-day study period were also assessed. The sample size was set at 80 subjects per group for feasibility reasons.
The primary safety endpoint was the incidence of primary intracranial bleeding or blood transfusion (whole blood or packed red cells) during the 30-day study period.
In total, 333 subjects were randomised at 24 centres in 6 countries. The all-treated data set (all subjects randomized who received at least one dose of study drug) consisted of 326 subjects (fondaparinux 4mg: 81 subjects; fondaprinux 8mg: 77 subjects; fondaparinux 12mg: 83 subjects; UFH: 85 subjects). A total of 10 (3.1%) subjects with protocol deviations were excluded from the main efficacy analysis at 90 minutes and 127 subjects (39.0%) with protocol deviations were excluded from the main efficacy analysis on Day 6±1.

Results:
There was no significant dose effect of fondaparinux on the number of subjects with TIMI Grade 3 flow assessed at 90 minutes (fondaparinux 4mg: 64.6%; fondaparinux 8mg: 68.9%; fondaparinux 12mg: 59.5%; UFH: 67.9%) or at Day 6±1 (fondaparinux 4mg: 81.3%; fondaparinux 8mg: 88.0%; fondaparinux 12mg: 88.9%; UFH: 75.0%). The incidences of individual clinical endpoints (death, MI and revascularisation) were not statistically significant between the four treatment groups.

There was no statistically significant trend for a dose-effect on the primary safety endpoint. The percentage of subjects with the primary safety endpoint during the 30±7 day study period was comparable in the four treatment groups (fondaparinux 4mg: 4.9%; fondaparinux 8mg: 9.1%; fondaparinux 12mg: 7.2%; UFH: 7.1%). There was a dose-dependent increase in unusual bleeding (as considered by the investigator) in the fondaparinux group (p=0.0006); the incidence in the fondaparinux 4mg group (24.7%) was lower than the fondaparinux 8mg (48.1%) and 12mg (51.2%) groups but similar to that with UFH (26.2%). Most of these bleeding events were procedural (site of femoral puncture for catheterisation). There were seven deaths, two in each of the fondaparinux groups and one in the UFH group. The incidence of SAEs and AEs leading to permanent treatment discontinuation were higher in the fondaparinux 8mg and 12mg groups compared with the 4mg and UFH groups.

Conclusion:
Based on the results of coronary angiography at 90 minutes and Day 6±1 and on the occurrence of clinical endpoints, the efficacy of fondaparinux in restoring coronary patency was considered comparable with that of UFH, when both agents were used in combination with rTPA and ASA. However, no dose effect was observed for early or late coronary patency or the clinical endpoints. The incidence of subjects with blood transfusions or intracranial bleeding was similar in the four treatment groups. However, the overall incidence of unusual bleeding indicated a dose-effect relationship.

Discussion on dose selection

The CHMP questioned the selection of the 2.5mg dose as it is not supported by a strong clinical rationale. Moreover, in contrast to LMWHs where the higher VTE treatment doses are approved for use in UA/NSTEMI, fondaparinux 2.5 mg is the same dose used for the prevention of VTE. However, unlike those conducted with fondaparinux, the phase II ACS studies for the LMWHs did not evaluate the wide dose range that included the lower VTE prevention doses.

The Applicant claims that despite the lack of a clear dose-response pattern in the phase II trials, the following important findings have been taken into account when selecting the 2.5mg dose:

- The data from PENTUA (UA/NSTEMI) and PENTYLASE (STEMI) suggested that the lowest doses in each (2.5mg and 4.0mg respectively) had comparable efficacy to their respective benchmark therapies enoxaparin and UFH.
- Although there was no clear evidence of a dose response relationship for the primary efficacy or safety endpoints in either study, there was evidence of a dose-dependent increase in unusual bleeding in PENTYLASE, suggesting that a minimally effective dose might be appropriate in order to reduce bleeding liability, particularly given the concomitant use of antiplatelet therapies

and interventions used in the ACS population. The selection of a common dose for both indications was considered appropriate given that UA, NSTEMI and STEMI represent a disease continuum with a common underlying pathophysiology.

- Although 4mg was the lowest dose common to both studies, bleeding data in PENTUA suggested that 2.5mg had the lowest bleeding risk of all the doses evaluated (including 4mg) and there was no suggestion of an efficacy advantage at doses higher than 2.5mg.

OASIS 5 study: fondaparinux in the treatment of UA/NSTEMI

This was a double-blind, double-dummy, parallel-group, controlled trial to compare the safety and efficacy of fondaparinux and enoxaparin in subjects with UA/NSTEMI and was conducted at 576 centres in 42 countries.

The *primary objective* of was to evaluate whether fondaparinux 2.5mg was "non-inferior", or superior to, enoxaparin in preventing death and ischemic events (MI or refractory ischemia [RI]) up to Day 9 in the acute treatment of subjects with UA/NSTEMI concurrently managed with standard medical therapy. As a non-inferiority study, the primary endpoint was assessed at the end of the treatment period (Day 9). This conservative approach was taken to avoid positive bias in favour of non-inferiority that might occur at remote time points due to factors unrelated to the short term therapy.

The *secondary objectives* were i) to determine whether fondaparinux is superior to enoxaparin in reducing death and MI at Day 9, ii) to determine whether fondaparinux is superior to enoxaparin in reducing major bleeding events up to Day 9, and iii) to determine if the relative effect on the primary endpoint, i.e., prevention of death, MI, or RI at Day 9, is sustained at Days 14, 30, 90, and 180.

The efficacy *endpoints* are shown in the table below:

	OASIS 5[1]
Primary outcome	• Death/MI/RI (at Day 9)
Secondary Outcomes	• Death/MI/RI (at Days 14, 30, 90, 180) • Death/MI (at Days 9, 14, 30, 90, 180) • Death, MI, or RI taken separately (at Days 9, 14, 30, 90, 180)
Other Outcomes	• Death/MI/stroke (at Days 9, 14, 30, 90, Day 180) • Stroke (at Days 9, 14, 30, 90, 180) • Severe Ischemia (at Days 9, 14, 30, 90, 180) • Non-fatal cardiac arrest (at Days 9, 14, 30, 90, 180) • Heart failure (during initial hospitalization) • Efficacy/Safety Balance outcome -Death/MI/RI, or major bleeding (at Days 9, 14, 30, 90, 180) -Death/MI/major bleeding (at Days 9, 14, 30, 90, 180)

The primary safety endpoint was the incidence of adjudicated major bleeding up to and including Day

9. Bleeding definitions used in the phase III studies are provided below.

Major Bleed	Protocol Definition[1]	Revised Definition[2]
Clinically-overt bleeding with ≥1 of the following:		
Fatal	+	+
Symptomatic intracranial hemorrhage	+	+
Retroperitoneal hemorrhage	+	+
Intraocular bleeding leading to signif. vision loss	+	+
Requiring surgical intervention		+
Any drop in Hb plus blood transfusion ≥3g/dL (with each blood transfusion unit counting for 1.0g/dL Hb)	+	
Any drop in Hb plus blood transfusion ≥3g/dL		+
Blood transfusion ≥2 units	+	+

Minor Bleed	Protocol Definition[1]	Revised Definition[3]
Clinically-significant non-major bleed with ≥1 of the following:		
Leading to ≥24hr interruption of study drug	+	+
Requiring surgical intervention	+	
Blood transfusion 1 unit	+	+

TIMI Severe Bleed	Protocol Definition[1]	Revised Definition[3]
At least 1 of the following:		
Fatal	+	+
Intracranial hemorrhage	+	+
Cardiac tamponade	+	+
Clinically-significant bleed with Hb drop >5g/dL (with each blood transfusion unit counting for 1.0g/dL Hb)	+	
Clinically-significant bleed with Hb drop >5g/dL		+

A single, independent Event Adjudication Committee (EAC) was responsible for blinded adjudication of all primary efficacy and safety outcome events, as well as key secondary events.

The comparator was enoxaparin, selected based on its common usage in the management of UA/NSTEMI as well as its class IIA recommendation in the American College of Cardiology (ACC)/American Heart Association treatment guidelines and the general recommendation in the European Society of Cardiology (ESC) guidelines. The dose regimen and treatment duration used is consistent with what is currently approved for UA/NSTEMI.

Subjects presenting within 24 hours with symptoms suspected to represent UA/NSTEMI, and, met one of the two following additional criteria were included:

- Troponin T or I or creatine kinase MB above the upper limit of normal
- ECG changes compatible with ischemia (i.e. ST depression at least 1mm in 2 contiguous leads or T wave inversion >3mm or any dynamic ST shift or transient ST elevation)

These criteria were modified during the conduct of the study in order to increase the blinded event rate to meet the projected sample size. This change required subjects <60 years to be higher risk and have both elevated cardiac enzymes and ECG changes consistent with ischemia.

The key *exclusion criteria* were: Subjects with severe renal insufficiency (i.e. serum creatinine ≥3mg/dl or 265µmol/l), a contraindication to low molecular weight heparin (LMWH), or who had already had a revascularisation procedure performed for the qualifying event.

Regarding *study treatments*, subjects received fondaparinux 2.5mg s.c once daily for 8 days or until hospital discharge, if earlier, or weight-adjusted enoxaparin (1mg/kg) twice daily for 2-8 days or until clinically stable, both administered in a double-blind double-dummy fashion. If creatinine clearance was between 20ml/min and 30ml/min, a once-daily 1mg/kg s.c. injection of enoxaparin or enoxaparin-placebo was administered at 24 hour intervals (± 4 hours). Subject follow-up was for a minimum period of 90 days and a maximum of 180 days. All subjects were to be followed for the pre-specified study period or until death.

For subjects undergoing CABG surgery, study drug administration was to be temporarily interrupted between 24 hours before and 48 hours after surgery.

For all *subjects undergoing PCI*, the study blind was maintained. All such subjects were to be pretreated with clopidogrel and ASA at least 6 hours before the procedure. If PCI was performed between randomisation and Day 8, and within 12 hours of the last s.c. dose of study drug, subjects were to receive additional study drug: fondaparinux 2.5 or 5 mg i.v. vs UFH 65 or 100 IU/kg i.v.

(enoxaparin group) depending on the time since the previous dose of s.c. study drug and whether i.v. GPIIb/IIIa inhibitor use was planned, administered at least 1 minute before insertion of the guiding catheter. Rescue open-label UFH in either treatment group was permitted based on the ACT result.

If PCI was performed as the initial treatment, subjects were to be treated with study drug for at least 2 calendar days.

Study drug administration was to be continued after PCI, whenever possible. If PCI was performed at any time during the follow-up period, the anti-coagulant regimen was at the investigator's discretion.

The following medications were not permitted concurrently with study drug administration: heparin and heparinoids (standard or LMWH), direct thrombin inhibitors, oral anti-coagulant drugs (vitamin K antagonists), fibrinolytic agents, dextrans. The use of NSAIDs was discouraged. When UFH or LMWH was administered prior to randomisation, study drug administration did not begin until after 2 or 6 hours, respectively.

Statistical analyses and sample size

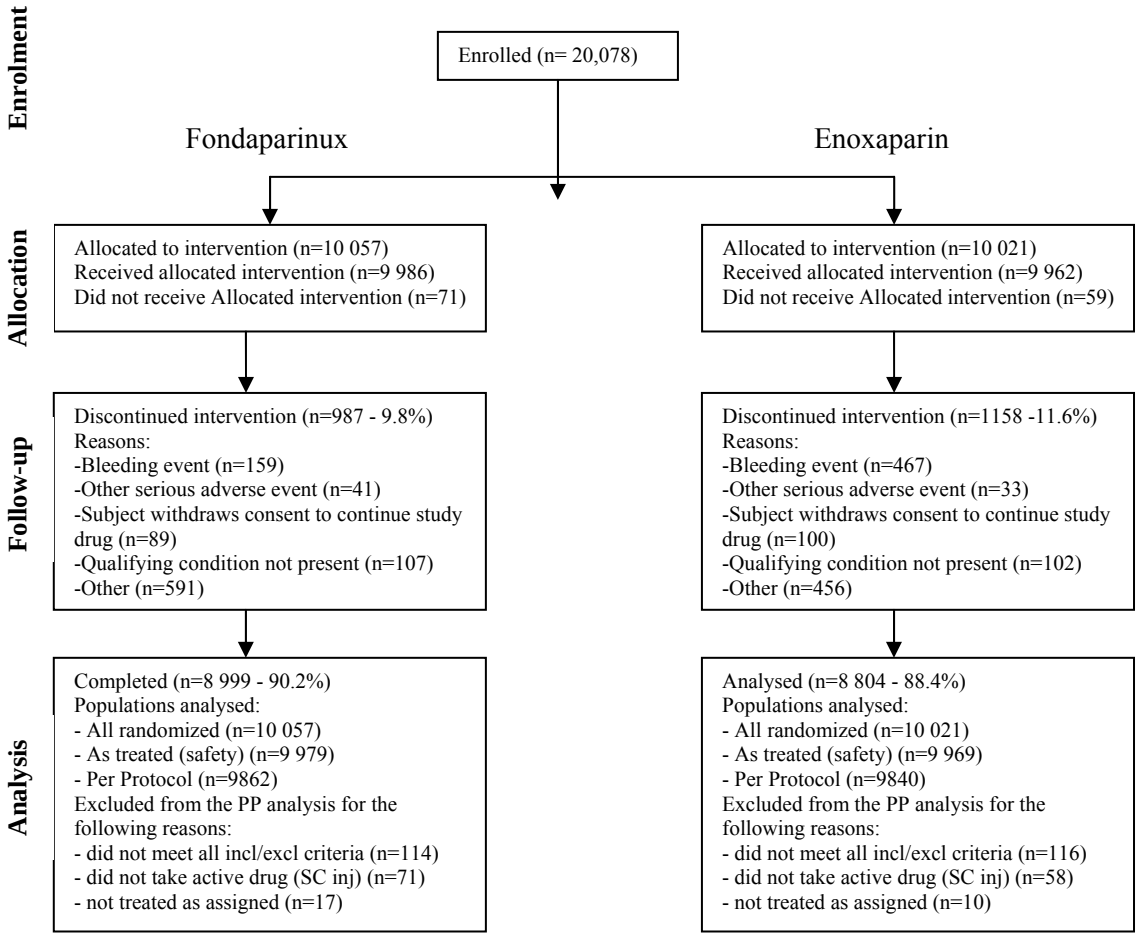
OASIS-5 was planned as a non-inferiority study with the option for a superiority approach. Fondaparinux was to be considered non-inferior to enoxaparin if the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio did not exceed the 1.185 non-inferiority margin (i.e. delta). In addition, if this upper limit did not exceed 1, fondaparinux was to be considered statistically superior to enoxaparin. The possible switch to superiority testing would not introduce multiplicity testing due to the nature of this closed testing procedure. The non-inferiority margin was derived from a meta-analysis of studies that demonstrated the benefit of adding UFH or LMWH as short-term treatment in ASA-treated subjects [Eikelboom, 2000]. The rationale for applying the 1.185 non-inferiority margin (derived from the composite of death or MI) to the triple outcome of death, MI, or RI is supported by FRISC I [Fragmin during Instability in Coronary Artery Disease (FRISC) study group, 1996]. In that study, there was a similar impact at Day 6 of LMWH vs placebo on the double endpoint of death or MI (relative risk [RR] 0.37, 95% CI 0.20;0.68) and the triple endpoint of death, MI or revascularisation for refractory/recurrent ischemia (RR 0.38, 95% CI 0.22;0.66).

The study was to be completed when 1,414 subjects with primary events were observed. Based on an expected pooled event rate of approximately 7%, 20,000 subjects would be required, which would provide at least 85% power.

Efficacy outcomes were evaluated in the "all randomised" population, the purest intent-to-treat (ITT) population, and a per protocol (PP) analysis was also performed. The primary efficacy variable was analysed using a Cox proportional hazards model, with treatment group as the only dependent variable. To investigate the consistency of the treatment effect across the strata, analyses were also performed for each stratum individually. In addition, the interaction of treatment effect with strata was investigated using a Cox proportional hazards model with terms for treatment group, strata (as a covariate) and the treatment by strata interaction. All safety analyses were performed on the "as treated" (safety) population (those who received at least 1 dose of study medication and analysed according to the treatment actually received). The primary safety endpoint of adjudicated major bleeding was also analysed by using the "all randomised" population, as specified in the protocol.

Results

More than 99% of the 20,000 subjects enrolled received treatment and the majority completed the protocol-defined treatment period. Following is a figure depicting the participant flow.



Regarding *baseline characteristics*, there were no notable differences between treatment groups in terms of baseline demographic or clinical characteristics, cardiovascular history, or time between onset of qualifying episode of chest pain/symptoms and randomisation. There were similar proportions of patients enrolled with UA (45%) or NSTEMI (55%) between the two arms. In general, most of the patients were treated according to the current standards: ASA 98%, clopidogrel 62%, ACE 70%, statins 78%, beta-blockers 87%, nitrates 80%. The concomitant use of medications was similar between groups. In terms of clinical interventions, 63% of the patients underwent coronary angiographies, which reflects an adequate management of ACS according to current clinical standards, and 34% of patients had PCI following UA or NSTEMI. This represents an important subgroup of patients. The percentage of patients that benefited from PCI corresponds to the usual practice; the results in this subgroup are of importance and are detailed in the corresponding sections of this report.

Regarding the results of the *primary endpoint,* OASIS-5 met its primary objective of demonstrating that fondaparinux was non-inferior to enoxaparin in the acute treatment (median 5-6 days) of subjects with UA/NSTEMI in the early prevention of adjudicated death, MI or RI at Day 9. The upper bound of the 95% CI (1.13) was well within the pre-defined 1.185 margin. The one-sided non-inferiority p-value was 0.003 and the upper bound of the 99% CI was 1.17. Importantly, the non-inferiority conclusion was also evident in the more conservative PP population, in which the hazard ratio and upper bound of the 95% CI were identical to those of the All Randomised population. In addition, several sensitivity analyses on the primary endpoint were conducted which supported the conclusions of non-inferiority, indicating the robustness of the findings.

Table 1 Proportional hazards analysis of the first occurrence of adjudicated death, MI or RI up to and including Day 9

	Fondaparinux	Enoxaparin
All Randomised	**n=10,057**	**n=10,021**
Events	579 (5.8%)	574 (5.7%)
Hazard Ratio (Fondaparinux vs Enoxaparin)	1.01	
95% CI	(0.90, 1.13)	
Hazard Ratio p-value	0.923	
Per Protocol	**(n=9862)**	**(n=9840)**
Events	566 (5.7%)	561 (5.7%)
Hazard Ratio (Fondaparinux vs Enoxaparin)	1.01	
95% CI	(0.90, 1.13)	
Hazard Ratio p-value	0.903	

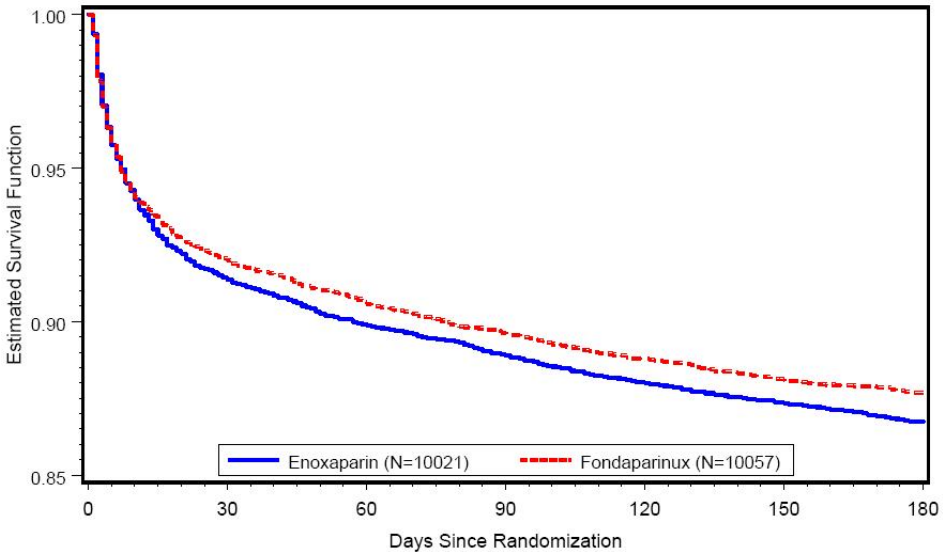
Regarding secondary outcomes, there was evidence of a modest, non-significant reduction in the risk of death/MI/RI favouring fondaparinux, initially evident at Day 14 and sustained up to Day 180.

Table 2 Summary of the Proportional Hazards Analysis Death/Myocardial Infarction or Refractory Ischemia at All Time points - All Randomised Population.

Death/MI/RI Timepoint	Fondaparinux n=10,057 (%)	Enoxaparin n=10,021 (%)	HR (95% CI)	p-value
Day 14	658 (6.5%)	701 (7.0%)	0.94 (0.84, 1.04)	0.220
Day 30	806 (8.0%)	865 (8.6%)	0.93 (0.84, 1.02)	0.126
Day 90	1044 (10.4%)	1112 (11.1%)	0.93 (0.86, 1.02)	0.110
Day 180	1223 (12.2%)	1309 (13.1%)	0.93 (0.86, 1.00)	0.063

There was a tendency to areduction in the risk of the primary endpoint at all time points in the fondaparinux group relative to the enoxaparin group, as suggested by the separation in the Kaplan-Meier curves below.

Kaplan-Meier Plot of Time to first occurrence of adjudicated death, MI or RI



While the incidence of the primary endpoint was similar in both treatment groups at Day 9 (primary time point), a 6% reduction in favour of fondaparinux was observed at Day 14. The benefit observed with fondaparinux was sustained at Days 30, 90, and 180 with a consistent 7% risk reduction.

The results of the individual components of the primary endpoint at Day 9 are shown below.

Table 3 Overview of **Primary Outcome Components at Day 9** in OASIS 5 (All Randomised population)

Outcome, n(%)	**Fondaparinux** N=10,057	**Enoxaparin** N=10,021	HR (95% CI)	p-Value
Death/MI/RI	579 (5.8)	574 (5.7)	1.01 (0.90, 1.13)	0.923
Death/MI	409 (4.1)	412 (4.1)	0.99 (0.86, 1.13)	0.879
Death	177 (1.8)	186 (1.9)	0.95 (0.77, 1.17)	0.614
MI	263 (2.6)	264 (2.6)	0.99 (0.84, 1.18)	0.935
RI	194 (1.9)	189 (1.9)	1.02 (0.84, 1.25)	0.821

There was a consistent favourable trend in each of the components of the composite primary endpoint that persisted up to Day 180 (results not shown). The incidence of adjudicated MI was numerically similar between groups at Day 9, but then appears to be lower in the fondaparinux group compared to the enoxaparin group from Day 14 onwards (results not shown). The proportion of subjects experiencing RI (as adjudicated) was similar in both treatment groups at all time points.

The results of adjudicated death at all time points are shown below.

Table 4 - Summary of the Proportional Hazards Analysis of **Adjudicated Death at All Time points**

Death Timepoint, n (%)	**Fondaparinux N=10,057**	**Enoxaparin N=10,021**	**HR (95% CI)**	**p-Value**
Day 9	177 (1.8%)	186 (1.9%)	0.95 (0.77, 1.17)	0.614
Day 14	211 (2.1%)	242 (2.4%)	0.87 (0.72, 1.04)	0.135
Day 30	295 (2.9%)	352 (3.5%)	0.83 (0.71, 0.97)	0.022
Day 90	460 (4.6%)	510 (5.1%)	0.90 (0.79, 1.02)	0.089
Day 180	574 (5.7%)	638 (6.4%)	0.89 (0.80, 1.00)	0.052

Fondaparinux was associated with a reduction in all-cause mortality relative to enoxaparin. Although the incidence of death was similar in the two treatment groups at Day 9, a clinically meaningful risk reduction of 13% in favour of fondaparinux was observed at Day 14. By Day 30, fondaparinux was associated with a statistically significant 17% reduction in the risk of all-cause mortality. The mortality benefit observed with fondaparinux was consistent and sustained at Day 90 and 180 with 10% and 11% risk reductions, respectively with the upper bounds of the 95% CI's close to unity.

The event rates for all adjudicated strokes were low at all time points, with the incidence of stroke numerically lower in the fondaparinux group. By Day 180, there was a 22% reduction in the risk of stroke (p=0.039). This relative benefit appeared to be due to a reduction in ischemic rather than haemorrhagic strokes.

Table 5 Proportional hazards analysis of adjudicated stroke at all time points - All Randomised population

Stroke Time point	**Fondaparinux n=10,057 (%)**	**Enoxaparin n=10,021 (%)**	**HR (95% CI)**	**p-value**
Day 9	37 (0.4%)	45 (0.4%)	0.82 (0.53, 1.27)	0.370
Day 14	50 (0.5%)	60 (0.6%)	0.83 (0.57, 1.21)	0.331
Day 30	74 (0.7%)	95 (0.9%)	0.77 (0.57, 1.05)	0.099
Day 90	108 (1.1%)	128 (1.3%)	0.84 (0.65, 1.08)	0.175
Day 180	127 (1.3%)	161 (1.6%)	0.78 (0.62, 0.99)	0.039

The composite secondary end-point death, MI or stroke was reduced by 11% at Day 180 (p=0.007).

Subgroup analyses

No significant interactions were found according to age, sex, BMI or Creatinine Clearance; OASIS-5 seems to have a satisfactory internal consistency with a rather homogeneous response across the usual patient subgroups.

Analyses of the primary outcome were also performed by anticoagulant treatment received (prior heparin use and concomitant anti-coagulant), by qualifying Diagnosis and by PCI and CABG Surgery. An excess event rate was observed at Day 9 in both treatment groups based on prior use of heparin and concomitant use of thienopyridines or i.v. GPIIb/IIIa compared to the sub groups not receiving these agents. These results are consistent with the greater use of these therapies in higher risk patients.

Regarding concomitant interventions (PCI in 34% of the included patients or CABG surgery in 10%), results on the primary endpoint showed that the percentage of events was twice higher in patients undergoing PCI and CABG compared to patients that did not undergo these interventions.
The overall response on the primary composite end point is not homogeneous across the group of patients undergoing or not PCI, as shown below.

Table 6. Proportional Hazards Analysis of the First Occurrence of Death/MI/RI Up to and Including Day 9 by PCI usage. All Randomized Population

	Number Events/Number Analysed (%)				
Covariate Category	**Fondaparinux**	**Enoxaparin**	**HR (95% CI)**	**Covariate p-value**	**Treatment by Covariate Interaction p-value**
PCI					
Overall	579/10,051 (5.8%)	574/10,020 (5.7%)	1.01 (0.90, 1.13)[1]	< 0.001	0.232
No	274/6597 (4.2%)	292/6585 (4.4%)	0.94 (0.79, 1.10)		
Yes	305/3454 (8.8%)	282/3435 (8.2%)	1.08 (0.92, 1.27)		

1. Hazard ratio and 95% CI's are adjusted for strata and the covariate of interest.

At day 9, in the group of patients not having PCI, the point estimate is in favour of fondaparinux (4.2 % versus 4.4%); in PCI patients the point estimate is in favour of enoxaparin [8.2% versus 8.8%; HR 1.08 (0.92, 1.27)]. This divergent response is still apparent at Day 30. In PCI patients, the incidence of events occurring between the day of PCI and Day 30 was 8.6% on fondaparinux versus 8.4% on enoxaparin.. When considering the components of the composite end point, in the PCI group, there is a higher rate of MI, death being equal in the two groups (at Day 9, MI/death 5.7% fondaparinux versus 5.4% enoxaparin and death 1.1% in both groups). The treatment by covariate interaction (PCI and no-PCI subgroups) is non-significant (p=0.232), however due to the known low power of the test, this lack of interaction is not entirely reassuring. The heterogeneous efficacy response across this important subgroup of patients is of concern and is consistent with the complications during PCI in the fondaparinux patients, further detailed in the safety section below.Stent deployment during PCI was high (approximately 90% of patients), with bare metal stents predominating. This pattern was common across the majority of countries.
Clopidogrel was administered in 70% and 59% of PCIs in OASIS 5 and 6, respectively. The median pre-PCI dose of clopidogrel was 75mg in OASIS 5 and 300mg (i.e. a loading dose) in OASIS 6, consistent with the difference in the timing of when the procedure is conducted relative to diagnosis in the two study populations.

Table 7. The Number and Percent of Subjects Experiencing Adjudicated Events from the Day on which PCI was conducted up to Day 30. All Randomized Population

	PCI in 8 Days While on Study Drug[1]		**All Randomized Subjects**	
	Fondaparinux (N=2854)	Enoxaparin (N=2741)	Fondaparinux (N=10057)	Enoxaparin (N=10021)
Death/MI/RI	246 (8.6%)	230 (8.4%)	806 (8.0%)	865 (8.6%)
Death	56 (2.0%)	60 (2.2%)	295 (2.9%)	352 (3.5%)
MI	150 (5.3%)	134 (4.9%)	387 (3.8%)	411 (4.1%)
RI	65 (2.3%)	64 (2.3%)	221 (2.2%)	223 (2.2%)

1. Only events that occurred on the Day of PCI up to Day 30 are counted.

Safety in OASIS-5

Patient exposure is summarised in the table below

Table 8 Summary of treatment completion status and reasons for withdrawal from active study drug

	Fondaparinux (N=10057)	Enoxaparin (N=10021)
Not Treated	71 (0.7%)	59 (0.6%)
Treated	9986 (>99%)	9962 (>99%)
Completion Status of Treated Subjects		
Completed Study Drug	8999 (90.2%)	8804 (88.4%)
Early Permanent Discontinuation	987 (9.8%)	1158 (11.6%)
Reason for Early Permanent Discontinuation		
Bleeding Event	159 (1.6%)	467 (4.7%)
Other Serious Adverse Event	41 (0.4%)	33 (0.3%)
Subject withdraws consent to continue study drug	89 (0.9%)	100 (1.0%)
Qualifying condition not present	107 (1.1%)	102 (1.0%)
Other	591 (5.9%)	456 (4.6%)

Approximately 10% of patients discontinued the study in both groups. Discontinuation for bleeding events was higher in enoxaparin (4.7%) than in fondaparinux group (1.6%), and discontinuation for other reasons was higher in fondaparinux (5.9%) than in enoxaparin group (4.6%).

Bleeding

Following is a table summarising the main bleeding events.

Table 9 Summary of bleeding events as reported by the investigator on therapy and up to and including day 9: as treated safety population.

	Fondaparinux (N=9979)	Enoxaparin (N=9969)
Day 9		
Any event	**440 (4.4%)**	**977 (9.8%)**
Major bleed	205 (2.1%)	410 (4.1%)
Fatal	7 (0.07%)	22 (0.2%)
Symptomatic intracranial haemorrhage	7 (0.07%)	7 (0.07%)
Retroperitoneal haemorrhage	9 (0.09%)	36 (0.4%)
Intraocular bleeding (leading to significant vision loss)	0	0
Any drop in Hb plus blood transfusion ≥ 3g/dl	189 (1.9%)	385 (3.9%)
Blood transfusion ≥ 2 units	156 (1.6%)	280 (2.8%)
Minor bleed	115 (1.2%	320 (3.2%)
Any bleed (major or minor)	314 (3.1%)	721 (7.2%)
Other bleed*	128 (1.3%)	270 (2.7%)
TIMI severe bleed	148 (1.5%)	260 (2.6%)
Type of bleeding		
CABG related bleed	86 (0.9%)	72 (0.7%)
PCI related bleed	82 (0.8%)	183 (1.8%)
On therapy		
Any event	**410 (4.1%)**	**959 (9.6%)**
Major bleed	180 (1.8%)	393 (3.9%)
Fatal	7 (0.07%)	21 (0.2%)
Symptomatic intracranial haemorrhage	5 (0.05%)	7 (0.07%)
Retroperitoneal haemorrhage	8 (0.08%)	35 (0.4%)
Intraocular bleeding (leading to significant vision loss)	1 (0.01%)	0
Any drop in Hb plus blood transfusion ≥ 3g/dl	165 (1.7%)	369 (3.7%)
Blood transfusion ≥ 2 units	133 (1.3%)	266 (2.7%)

Minor bleed	109 (1.1%)	318 (3.2%)
Any bleed (major or minor)	286 (2.9%)	705 (7.1%)
Other bleed*	126 (1.3%)	268 (2.7%)
TIMI severe bleed	128 (1.3%)	248 (2.5%)
Type of bleeding		
CABG related bleed	69 (0.7%)	62 (0.6%)
PCI related bleed	77 (0.8%)	182 (1.8%)

* "other bleeding" included any clinically-significant bleeding reported by the investigator that did not meet the criteria of a major or minor bleed.

Adjudicated major bleeding occurred in 2.1% of fondaparinux subjects and 4.1% of enoxaparin subjects in the All Randomised population, translating into a 48% lower risk of major bleeding with fondaparinux ($p<0.001$). The results for the As Treated population (safety population) were virtually identical to those observed for the All Randomized population.

On-therapy, similar results were observed in the safety population. Adjudicated major bleed occurred with incidence of 3.9% in enoxaparin and 1.8% in fondaparinux group.

Severe bleeding complications according to the TIMI criteria were reported at day 9 in 2.6% in enoxaparin group compared to 1.5% in fondaparinux group. The incidences of bleeding as reported by the investigator were also consistent with those observed in adjudicated major bleed and severe bleeding according to the TIMI criteria (1.5% vs 2.6% in fondaparinux and enoxaparin, respectively).

Clinical implication of bleeding

Subjects who had a major or minor bleeding during hospitalisation had a significantly higher rate of death at day 30 than subjects without a bleeding event, regardless of treatment group. Two *ad-hoc* analyses were performed by the Applicant to assess the clinical implications of bleeding and to investigate whether the difference in mortality between the treatment groups observed at the end of the study may be related to the lower rate of bleeding with fondaparinux.

The first analysis looked at the rate of death up to Day 30 in patients who experienced a major/minor bleeding event up to day 9 compared to the overall population.

Table 10 Incidence of death by day 30 in subjects who experienced a bleeding event by day 9: All randomised population.

	Incidence of Death by Day 30, n/N (%)	
Subjects	**Fondaparinux**	**Enoxaparin**
Overall All Randomized Population	295/10,057 (2.9%)	352/10,021 (3.5%)
With Adjudicated Major Bleed up to Day 9	24/214 (11.2%)	56/408 (13.7%)
With "Any Bleed"[1] up to Day 9	39/448 (8.7%)	85/980 (8.7%)

There was a higher incidence of death in patients who experienced a bleeding event compared to the overall randomised population in both groups, and the highest incidence of death was reported in patients who experienced a major bleed. No difference was reported between fondaparinux group and enoxaparin group regarding death in patients who experienced "any bleed" (8.7% in both groups), however a small increase was reported in enoxaparin patients who experienced a major bleed than fondaparinux patients (13.7% vs 11.2% respectively).

The second analysis looked at patients who died up to day 30, in order to determine what proportion of patients had experienced a clinically important bleeding event up to day 9.

Table 11 Incidence of bleeding events up to and including day 9 in subjects who died by day 30: As treated population

Subjects	Fondaparinux	Enoxaparin
	Major Bleeding up to Day 9, n/N (%)	
Overall As Treated Population	209/9979 (2.1%)	406/9969 (4.1%)
Who died up to Day 30	32/290 (11.0%)	64/350 (18.3%)
	Any Bleeding[1] up to Day 9, n/N (%)	
Overall As Treated Population	439/9979 (4.4%)	976/9969 (9.8%)
Who died up to Day 30	43/290 (14.8%)	80/350 (22.9%)

1: any bleeding: major or minor bleed as reported by investigator.

In both treatment groups, patients who died by day 30 experienced numerically higher rates of bleeding up to and including day 9, compared to the overall as treated study population. A higher incidence of bleeding in patients who died by day 30 was observed in enoxaparin group compared to fondaparinux group.

Serious Adverse Events (SAEs) were reported in 4% (360/9979) in fondaparinux group and 5% (520/9969) in enoxaparin group. The most frequent on-therapy SAEs were puncture site haemorrhage (0.35% in fondaparinux vs 1.8% in enoxaparin), catheter-related complications (0.34% vs 0.11% respectively), post-procedural haemorrhage (0.34% vs 0.23% respectively) and coronary artery thrombosis (0.16% vs 0.05%).

Deaths

Events resulting in death were reported as a component of the primary efficacy endpoint and were not intended to be reported as SAEs. However, 215 out of the 1,212 deaths reported in the primary efficacy results were reported as fatal SAEs, of which 102 deaths (1.02%) occurred with fondaparinux (27 (0.27%) occurred while on therapy) and 113 (1.13%) with enoxaparin (38 (0.38%) while on therapy). The causes of death were similar in both groups, with an exception regarding coronary artery thrombosis which occurred only in fondaparinux patients and digestive haemorrhage which were more frequent in enoxaparin on therapy.

Death up to day 30 was numerically increased in enoxaparin group with 0.7% (66/9969) compared to 0.5% (54/9979) in fondaparinux group.

GI haemorrhage (3 vs 2), retroperitoneal haemorrhage (4 vs 0), haemorrhagic shock (2 vs 0), haematoma nos (1 vs 0) and haemorrhage NOS (1 vs 0) were more frequent in enoxaparin group.

Intracranial haemorrhage, including haemorrhagic stroke, were similar in both group (4 patients each).

SAEs other than death

A total of 819 patients experienced a SAE; 3.34% (334/9979) occurred in fondaparinux group and 4.85% (485/9969) in enoxaparin group. Of which 1.6% (163/9979) in fondaparinux group and 2.8% (285/9969) in enoxaparin were drug-related.

Drug-related catheter related complications (0.27% vs. 0.05%) and coronary artery thrombosis (0.14% vs 0.04%) were more frequent with fondaparinux. Other drug-related bleeding SAEs were more frequent with enoxaparin than with fondaparinux group: puncture site haemorrhage (1.00% vs. 0.29%), injection site haemorrhage (0.16% vs. 0.01%) retroperitoneal haemorrhage (0.16% vs. 0.05%), retroperitoneal haematoma (0.08% vs 0) and vascular pseudoaneurysm (0.28% vs 0.12%).

Thrombocytopenia was reported as a SAEs in 7 patients in fondaparinux and 9 in enoxaparin up to day 30, of which 5 (0.07%) on fondaparinux and 7 (0.09%) on enoxaparin occurred during the on-therapy period. Three patients experienced HIT in fondaparinux group. All patients underwent a CABG surgery, and one of them underwent a coronary angiography before the CABG surgery. Two patients received LMWH during the 7 days before randomisation and UFH during the initial hospitalisation as well as fondaparinux for 8 days. The third patient received a single dose of fondaparinux and enoxaparin-placebo on day 1 and a second dose of enoxaparin-placebo on day 2; he experienced thrombocytopenia and HIT on the fourth day. Normal platelet count was reported for all patients. It

was unknown for all patients whether they received UFH during surgery. HIT test was positive in two patients and not reported in one. In one case the patient received a platelet infusion. The outcome was favourable for all patients. HIT was assessed as non-related to fondaparinux.

Discontinuation

Discontinuation due to AEs occurred in 115 (1.15%) patients in fondaparinux group and 150 in enoxaparin group (1.50%). Discontinuation in fondaparinux group was due to: renal insufficiency (0.08% in fondaparinux vs 0.01% in enoxaparin), cardiac disorders including rhythm disorders, angina pectoris and coronary stenosis and thrombosis (0.19% vs 0.17% respectively), skin disorders including allergic dermatitis and rash (0.06% vs 0.03% respectively).

Discontinuation in enoxaparin group was due to vascular disorders including vascular pseudoaneurysm and haematoma (0.33% vs 0.21%) GI disorders mainly bleeding events (0.14% in enoxaparin vs 0.07% in fondaparinux respectively), general disorders including puncture site haemorrhage, catheter site haemorrhage and pyrexia (0.19% vs 0.07% respectively).

Other Adverse Events (AEs)

A total of 24% of patients in fondaparinux group experienced an AE compared to 28% in enoxaparin group. The following AEs were reported with similar incidence in both groups: headache, pyrexia, chest pain, dizziness, atrial fibrillation, and anaemia. Of these, headache, chest pain and atrial fibrillation were reported in at least 1% of subjects on fondaparinux.

The following AEs were more frequent in enoxaparin group than in fondaparinux group: puncture site haemorrhage (1.23% vs 0.37%), haematoma (0.79% vs 0.59%), vascular pseudo aneurysm (0.77% vs 0.4%) and increased hepatic enzymes (0.16% vs 0.05%). The followings AEs were more frequent in fondaparinux group than in enoxaparin: angina pectoris including post-infarction angina, unstable angina and Printzmetal angina (0.8% vs 0.5%), coronary artery thrombosis (0.17% vs 0.06% respectively), and catheter-related complications (0.34% vs 0.11% respectively).

Thrombocytopenia occurred in 1.2% (12) fondaparinux group, and in 1.7% (17) enoxaparin group. One patient experienced pancytopenia in fondaparinux group, and 1 patient experienced thrombocytemia in enoxaparin group.

Four patients experienced HIT in fondaparinux patients during the period including day 30, of which one occurred during the on therapy period. Three of these cases were serious and are described under section “SAEs other than death”.

Safety in special populations

Fondaparinux had a lower risk of major bleeding compared to enoxaparin regardless of sub-group, demonstrating the robustness of this clinically-important finding. Expectedly, the incidence of major bleeding in both treatment groups increased with known risk factors such as to age, female gender and decreased creatinine clearance. The incidence of major bleeding in fondaparinux subjects increased with decreasing body weight, although it should be noted that the number of events and subjects in the <50kg subgroup was small (<1%). This increase was not evident in enoxaparin subjects; however, the enoxaparin dose regimen utilized weight adjustment.

As expected, the incidence of bleeding was higher in patients taking concomitant anti-platelet, heparin, GPIIb/IIIa. An exception was noted for patients who were not taking ASA, where major bleeding was more frequent compared to those with concomitant ASA. This finding should be taken with caution, as only a small number of patients were not taking concomitant ASA. No difference was noted in fondaparinux group regarding PCI procedure; however, in enoxaparin group a higher incidence was noted in patients undergoing a PCI procedure compared to those who did not. Finally, the incidence of major bleeding was higher but similar in both treatment groups in patients who had undergone a CABG surgery.

Safety during PCI

The incidence of peri-procedural complications in subjects who underwent PCI while receiving active study drug was similar between the treatment groups (15.9% vs. 17.3% of PCIs performed, for fondaparinux and enoxaparin, respectively) and is shown in the table below.

Table 12 Complications during PCI. All Randomised Subjects Receiving PCI during Initial Hospitalisation and Within 8 Days of Randomisation and Were Receiving Study Drug (Subset 2)

	Fondaparinux (N=2854)	**Enoxaparin (N=2741)**
Number of PCIs performed	2888	2781
Any complication	460 (15.9%)	480 (17.3%)
Vascular site complications overall	93 (3.2%)	201 (7.2%)
Pseudoaneurysm requiring closure	30 (1.0%)	48 (1.7%)
Large haematoma	48 (1.7%)	132 (4.7%)
AV fistula	8 (0.3%)	1 (<0.1%)
Other vascular site complications	7 (0.2%)	20 (0.7%)
Other (i.e. coronary) complications during PCI	367 (12.7%)	279 (10.0%)
Abrupt closure of coronary artery	49 (1.7%)	36 (1.3%)
New angiographic thrombus	91 (3.2%)	49 (1.8%)
Catheter thrombus confirmed by adjudication	29 (1.0%)	8 (0.3%)
Clinical events during PCI	77 (2.7%)	64 (2.3%)
Death	8 (0.3%)	11 (0.4%)
MI	59 (2.0%)	47 (1.7%)
Stroke	2 (<0.1%)	2 (<0.1%)
Other clinical event	8 (0.3%)	4 (0.1%)

1. Note: Values are number of events (not number of subjects). Percentages represent the proportion of events based on the number of procedures performed

Fondaparinux was associated with fewer vascular access site bleeding events compared to enoxaparin (3.2% vs. 7.2% of PCIs performed), which is consistent with the lower bleeding risk observed with fondaparinux in the overall population. This treatment difference in favour of fondaparinux was driven predominantly by large haematomas (1.7% vs. 4.7% of PCIs performed).

Worryingly however, coronary complications tended to occur more frequently with fondaparinux relative to enoxaparin (12.7% vs. 10.0% of PCIs performed). In addition to the more frequent guiding catheter thrombus (1.0% vs. 0.3%), more disturbing are the higher rates of coronary abrupt closure and new angiographic thrombus (respectively 1.7% and 3.2% in the fondaparinux group).

Vascular site bleeding is usually clinically manageable and less of a concern than coronary complications. The occurrence of catheter thrombus (unblinded), an unexpected AE during the course of the study, prompted an amendement of the study protocol to emphasise the correct administration of fondaparinux intravenously during the PCI and to reiterate that heparinised catheter flushes could be used..

Proposed management strategy for fondaparinux-treated patients undergoing PCI: Use of UFH

Acknowledging the observed complications in fondaparinux patients undergoing PCI observed in OASIS-5 and OASIS-6 (see later in this report) and aware of the fact that UA/NSTEMI patients treated with s.c. fondaparinux may need to undergo PCI, the Applicant proposes that they should not receive fonadaparinux as the sole anticoagulant during the procedure but rather be managed according to standard medical practice and in line with treatment guidelines, using UFH as the adjunct for the procedure. UFH is established in clinical practice and is recommended in the ESC guidelines as the anticoagulant of choice during PCI, with its primary function being the avoidance of thrombus formation on the PCI hardware and at the site of injury/plaque rupture in the coronary vessel. The use of adjunctive UFH during PCI to prevent thrombus formation in the PCI catheter is consistent with the following clinical data from 3,849 procedures performed in OASIS 5 and 6, plus recent *in vitro* data:

- There were no instances of guiding catheter thrombus reported in 1848 UFH-treated subjects in OASIS 6 who underwent primary PCI for the index event (1850 procedures), nor in 1849 subjects (1999 procedures) in both OASIS 5 and 6 who underwent PCI after the study drug treatment period and who were anticoagulated according to local practice (UFH expected)
- *In vitro* data have shown that thrombus formation induced by PCI catheters occurs via activation of the contact (intrinsic) pathway and is mediated by thrombin and inhibited by UFH. Due to its selectivity for factor Xa and inability to inhibit any residual thrombin, fondaparinux is unable to inhibit contact thrombosis in the presence of catheter. Not unexpectedly due to its specificity, higher concentrations of fondaparinux could not overcome thrombus formation induced by the catheter. Clinically-relevant doses of UFH or bivalirudin (a direct thrombin inhibitor) in the presence of fondaparinux were able to inhibit clot formation in presence of catheters.

- *Safety of UFH during PCI in Fondaparinux-treated Patients*

The CHMP expressed concern regarding the safety of the Applicant's proposed management of fondaparinux-treated patients undergoing PCI with adjunct open-label UFH, as this has not been has not been formally studied in UA/NSTEMI patients. Further to a request form CHMP, the Applicant has provided a detailed analysis of bleeding events in patients undergoing PCI with adjunct open label UFH included in the clinical development of fondaparinux – see below.

Table 13 Summary of Major Bleeding Events up to Day 9 in Subjects Undergoing PCI with Adjunct Open Label UFH in PENTUA, OASIS 5 and OASIS 6, Subset 2/All Treated Population

	Fondaparinux	**Control[1]**
Non-primary PCI in OASIS 6	6/238 (2.5%)	6/224 (2.7%)
PCI in PENTUA	2/61 (3.3%)	0/15 (0%)
PCI in OASIS 5	15/481 (3.1%)	37/447 (8.3%)
Primary PCI in OASIS 6	6/374 (1.6%)	5/316 (1.6%)

Note: All Treated Population for PENTUA; Subset 2 for OASIS 5 and 6
Note: Subset 2 = All Randomised Subjects Receiving PCI During Initial Hospitalisation and Within 8 Days of Randomization and Who Were Receiving Study Medication
Note: Percentages represent the proportion of events based on the number of procedures performed.
Note: Bleeding events occurred on or after day of PCI
1. Control was UFH or placebo in OASIS 6, and enoxaparin in PENTUA and OASIS 5

In fondaparinux-treated STEMI subjects undergoing non-primary PCI in OASIS 6 and receiving open-label UFH according to a protocol-defined algorithm and in line with the proposed management strategy (238 procedures), there was no evidence of an increased bleeding risk compared to control subjects (224 procedures). This low bleeding risk was consistently observed regardless of the time from the last dose of fondaparinux to the start of PCI. Further, there was a low risk of peri-procedural coronary complications and no catheter thrombus events in subjects who received UFH prior to the PCI, and comparable rates of death or recurrent MI up to Day 30 relative to control subjects.

A further 854 subjects received open-label UFH in conjunction with i.v. fondaparinux during PCI (OASIS 5; 481 procedures and primary PCI in OASIS 6; 374 procedures). In PENTUA, 61 UA/NSTEMI subjects receiving one of 4 fondaparinux doses (2.5, 4.0, 8.0 or 12.0 mg s.c. once daily) underwent PCI with adjunctive, open-label UFH administered within 24 hours of the previous fondaparinux dose (61 procedures), consistent with the proposed PCI management strategy.

In these 3 settings, based on experience in 916 PCIs, UFH does not appear to increase the risk of bleeding in fondaparinux subjects relative to control, even though the level of anticoagulation was greater than in the proposed management strategy. In addition, when administered before PCI, UFH appears to minimise the risk of catheter thrombus. In these cases, 2 events of catheter thrombus were reported in fondaparinux subjects, with one subject receiving a dose of UFH (5 IU/kg) and the other receiving 44 IU/kg without upfront GPIIb/IIIa inhibitors, which is lower than that recommended in the treatment guidelines. Thus, combining the catheter thrombus events that occurred in all PCIs performed in fondaparinux-treated patients receiving pre-procedural UFH, administered at doses

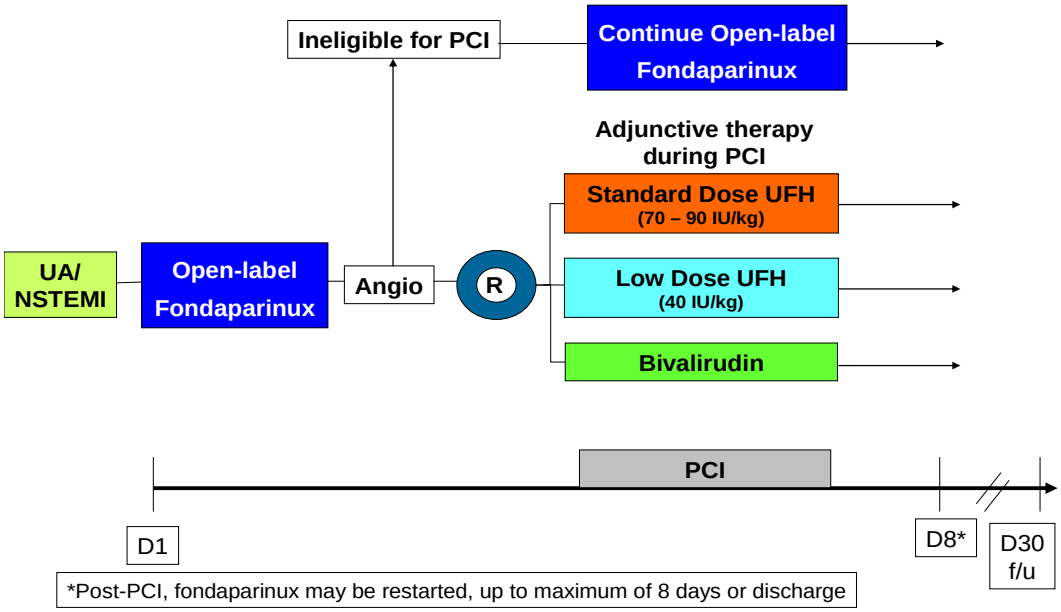
recommended in the treatment guidelines, there was only one reported event in 397 PCIs (0.25%). Notably, this rate is comparable to that seen in enoxaparin patients in OASIS 5.

The CHMP consulted with the SAG CVS whether the above evidence was sufficient to support the proposed switch to UFH during PCI both in terms of safety and efficacy. The SAG was of the opinion that the available evidence is insufficient to recommend the strategy proposed by the company. In particular, they were not convinced that the safety advantage with fondaparinux (over enoxaparin) would be maintained when the UFH is added in PCI patients and were of the opinion that a further study was required to address the doubts regarding the proposed switch to UFH during PCI procedure.

- *Post-Authorisation Safety (PASS) Study*

Acknowledging the limited safety experience of using UFH as an adjunct during non-primary PCI in fondaparinux, the Applicant proposes to carry out a PASS using the OASIS 5 inclusion/exclusion criteria (see figure below). The primary study objective will be to evaluate the safety in fondaparinux-treated patients undergoing PCI receiving adjunctive therapy with one of two regimens of i.v. UFH (standard and reduced dose) as the PCI adjunct in fondaparinux-treated patients. Secondary objectives will be i) to confirm that the rate of bleeding in fondaparinux-treated patients undergoing PCI receiving adjunctive therapy with UFH is comparable to that observed in OASIS 5, and ii) to evaluate the effectiveness of anticoagulation during PCI and clinical outcomes to 30 days.

Figure 1 Proposed PASS Design



The adequacy of the proposed PASS was discussed at length by the CHMP, particularly with regards as to whether the study should also look into the efficacy of the proposed use of UFH in fondaparinux-treated PCI patients. The CHMP sought the advice of the SAG CVS, who was of the opinion that the study should look into safety and efficacy and hence should be available in before the granting of the requested indication.

Further to the concerns of CHMP and the SAG, the Applicant submitted an alternative study design including an enoxaparin comparator. However, this comparative study design raises logistical difficulties due the timing of randomisation that inclusion of a comparator requires and necessitates the PCI population be evaluated via a sub-group analysis. More critically, the study raises issues on the population that should be included, given the difference in bleeding risk and long term efficacy outcomes favouring fondaparinux, as well as the new ESC guideline recommendation of fondaparinux over enoxaparin. The advantages and disadvantages of both study designs are summarised below.

Table14 Comparison of the Two PASS Designs

Current Study	Comparator (enoxaparin) Study
Advantages • Evaluates the most relevant patients based on the proposed indicated population • Randomised population includes only patients undergoing PCI **Disadvantages** • Limitations of a comparison to historical data	**Advantages** • Builds on existing data from OASIS 5 with enoxaparin **Disadvantages** • Requires restriction of the study population to exclude patients with a risk of bleeding - would not reflect the patients likely to receive fondaparinux in clinical practice and would underestimate the bleeding risk • i.v. enoxaparin during PCI would be necessary to comply with ESC recommendations – but is not approved by regulatory agencies • Evaluation in PCI patients would be a sub-group analysis.

Given the highlighted difficulties that would be encountered with the comparator (enoxaparin) study, the CHMP agrees that the PASS study proposed by the MAH is a satisfactory alternative.

OASIS-6: fondaparinux in the treatment of STEMI

This was a randomised, double-blind, parallel-group, controlled trial comparing the safety and efficacy of 2.5mg fondaparinux versus a control of usual care (UFH or Placebo) in subjects with STEMI.

The primary *objective* was to evaluate whether fondaparinux was superior to a control reflecting a usual care (UFH or placebo) in preventing death or recurrent MI (re-MI) up to Day 30 in subjects presenting with STEMI. The secondary efficacy objectives were to evaluate whether there was a beneficial effect of fondaparinux compared to control in preventing death or re-MI (Days 9, 90 and 180) and to evaluate whether fondaparinux was superior to control in preventing death, re-MI and refractory ischemia (Day 30).

Regarding *treatment allocation*, subjects were randomised to one of two strata based on the reperfusion strategy (indication for UFH or not) selected by the investigator prior to randomisation. Study drug was to be administered as soon as possible after randomisation.

- Stratum 1: no indication for UFH;

  Subjects who received a non-fibrin specific thrombolytic [e.g. streptokinase (STK)] prior to arrival in the ER were eligible for randomisation in Stratum 1 immediately, provided they did not meet the exclusion criterion with regard to heparin pre-randomisation.

  Treatment was fondaparinux 2.5mg i.v. bolus vs placebo just after randomisation, followed by fondaparinux 2.5mg s.c. or placebo for 8 days or until hospital discharge, whichever was earlier.

- Stratum 2: indication for UFH. A number of different scenarios were envisaged:

  - *Subjects treated with a Fibrin-Specific Thrombolytic OR not scheduled for Reperfusion Therapy (PCI or Thrombolytic)*

    Immediately prior (approx. 15min) to start of thrombolytic therapy OR just after randomisation, patients received fondaparinux 2.5mg i.v. bolus vs. UFH 60 IU/kg (max 4000 IU) i.v. bolus, followed by fondaparinux 2.5mg s.c. for up to 8 days or discharge vs UFH i.v. 12 IU/kg/hr (max 1,000 IU/h) for 24 to 48 hours.

  - *Subjects undergoing Primary PCI*

    Immediately prior to procedure: fondaparinux 2.5 or 5 mg i.v. bolus vs UFH 65 or 100 IU/kg i.v. bolus, (depending on the upfront use or not of i.v. GPIIb/IIIa inhibitors, and on pre-

randomisation or not of UFH), followed by: fondaparinux 2.5mg s.c. or placebo for up to 8 days or discharge.

- *Subjects undergoing non-primary PCI (elective or rescue catheterisation) or CABG*

  In case of PCI after randomisation, the procedure was delayed where possible for 24 hours after the last s.c. fondaparinux/placebo injection and 3 hours after UFH/placebo infusion. The PCI was then performed as per local practice with open-label UFH and GPIIb/IIIa inhibitor.

  If PCI was performed <24 hours after the last injection of fondaparinux/placebo or within 3 hours after discontinuation of UFH/placebo, the subject was unblinded and treated with open-label UFH and GPIIb/IIIa inhibitors.

  The UFH/placebo infusion was not restarted, if possible, after the PCI. The first fondaparinux/
  placebo s.c. injection after the PCI, was 18-24 hours after the last fondaparinux/placebo s.c injection (pre-PCI) and at least 3 hours after sheath removal. The use of any GPIIb/IIIa after the PCI was left to the investigator's discretion.

  If CABG was required, study drug was temporarily interrupted preferably 24 hours prior to scheduled CABG surgery and restarted 48 hours post CABG, if possible.

Study drug was administered for up to 8 days on a background of standard care. Subject follow-up was for a minimum of 90 days and a maximum of 180 days, or until death.

OASIS 6 included subjects presenting within 12 hours (amended from 24 hours based on the results of the CREATE trial) with signs and symptoms of acute MI and definite ECG changes indicating STEMI [persistent ST-elevation (≥0.2mV in two contiguous precordial leads, or ≥0.1mV in at least two limb leads), or new left bundle branch block, or ECG changes indicating true posterior MI]. Eligible subjects included those with planned reperfusion with one of several thrombolytic agents (i.e., STK, urokinase, alteplase, reteplase, tenecteplase) or with primary PCI, as well as subjects who were not eligible for reperfusion therapy (e.g. late presentation or contra-indication to reperfusion therapy). The key *exclusion criteria* were: subjects with severe renal insufficiency (i.e. serum creatinine ≥3mg/dl or 265μmol/l), subjects who were currently receiving an oral anticoagulant agent with an INR >1.8, subjects who had LMWH or >5000IU UFH administered prior to randomisation, a contraindication to anticoagulant therapy such as high risk of bleeding or active bleeding and subjects who had pre-randomisation PCI for the index event or pre-randomisation rescue PCI.

Regarding *concomitant medication*, all subjects were to receive ASA OD (75-325mg) indefinitely. Furthermore subjects were concurrently managed with standard medical therapy such as nitrates, ACE inhibitors, β-blockers, anti-platelet agents (i.e. thienopyridines, GPIIb/IIIa inhibitors). Thrombolytics were allowed and were to be administered within 12 hours of the onset of symptoms. The concomitant use of LMWH, direct thrombin inhibitors or oral anticoagulants (i.e. vitamin K antagonists) during the treatment period was not allowed. In addition, UFH other than study medication or that permitted per protocol during non-primary PCI was not allowed.

The *primary efficacy endpoint* was the first occurrence of the composite of death (all-cause mortality) or re-MI at Day 30. Secondary efficacy endpoints included additional assessments of the primary endpoint at Days 9, 90 and 180 and the first occurrence of any component of the composite of death, recurrent MI or RI (as adjudicated) up to Days 9, 30, 90, and 180.

The *primary safety endpoint* was the first incidence of adjudicated severe haemorrhage (modified TIMI criteria) up to Day 9 – see definitions below.

	Protocol Definition[1]	Revised Definition[2]
Severe Hemorrhage (TIMI)		
Fatal hemorrhage	+	+
Symptomatic intracranial hemorrhage	+	+
Cardiac Tamponade	+	+
Decrease in Hb ≥5g/dL (with each blood transfusion unit counting for 1.0g/dL Hb)	+	
Decrease in Hb ≥5g/dL (not adding transfusions)		+
Minor Hemorrhage (TIMI)		
Decrease in Hb >3.0 to ≤5.0g/dL (with each blood transfusion unit counting for 1.0g/dL Hb)	+	
Decrease in Hb of >3.0 to≤5.0g/dL (not adding transfusions)		+
Major Bleeding		
Fatal	+	+
Symptomatic intracranial hemorrhage	+	+
Retroperitoneal hemorrhage	+	+
Intraocular hemorrhage leading to significant vision loss	+	+
Requiring surgical Intervention		+
Any decrease in Hb of ≥3.0g/dL (with each blood transfusion unit counting for 1.0g/dL of Hb),	+	
Any decrease in Hb of ≥3.0g/dL (not adding transfusions),		
Blood transfusion ≥2 unitsof red blood cells or equivalent of whole blood	+	+
Minor Bleeding		
Interruption of study drug for at least 24 hours	+	+
Surgical Intervention	+	
Transfusion of 1 unit of blood (whole blood or packed red blood cells)	+	+

1. Used for presentation of investigator reported bleeding events
2. Used by EAC and in presentation of adjudicated bleeding events

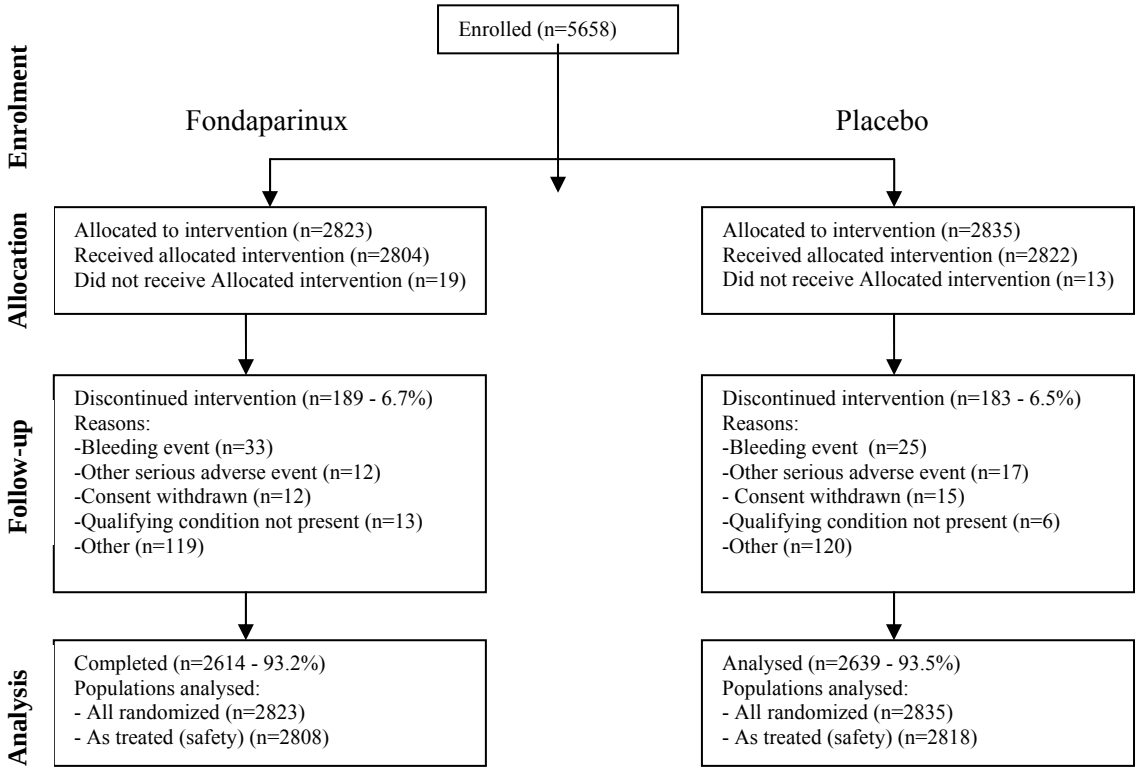
A *sample size* of 12,000 subjects allowed 84% power to detect a 15% difference in relative reduction in the hazard ratio given a control event rate of 12% with an alpha level of 5% (2-sided). All subjects randomised into the study ("All Randomised" population) were analysed in all safety and efficacy analyses. In addition, safety analyses were carried out according to the treatment subjects actually received ("As Treated" population). A subject was excluded from the "As Treated" population if they had no record of taking study medication. Protocol violations were examined to evaluate the quality of the study conduct; however, a "Per-protocol" population was not used for analysis in this study.

The primary efficacy variable was analysed using a Cox proportional hazards model for the overall population, stratified by indication of UFH. Fondaparinux was considered superior to control treatment if the upper limit of the two-sided 95% CI of the hazard ratio did not exceed 1 (corresponding to a p-value of 0.05). To investigate the consistency of the treatment effect across the strata, analyses were performed using a Cox proportional hazards model for each stratum individually, with treatment group as the only dependent variable. In addition, the interaction of treatment effect with strata was investigated using a Cox proportional hazards model with terms for treatment group, strata (as a covariate) and the treatment by strata interaction.

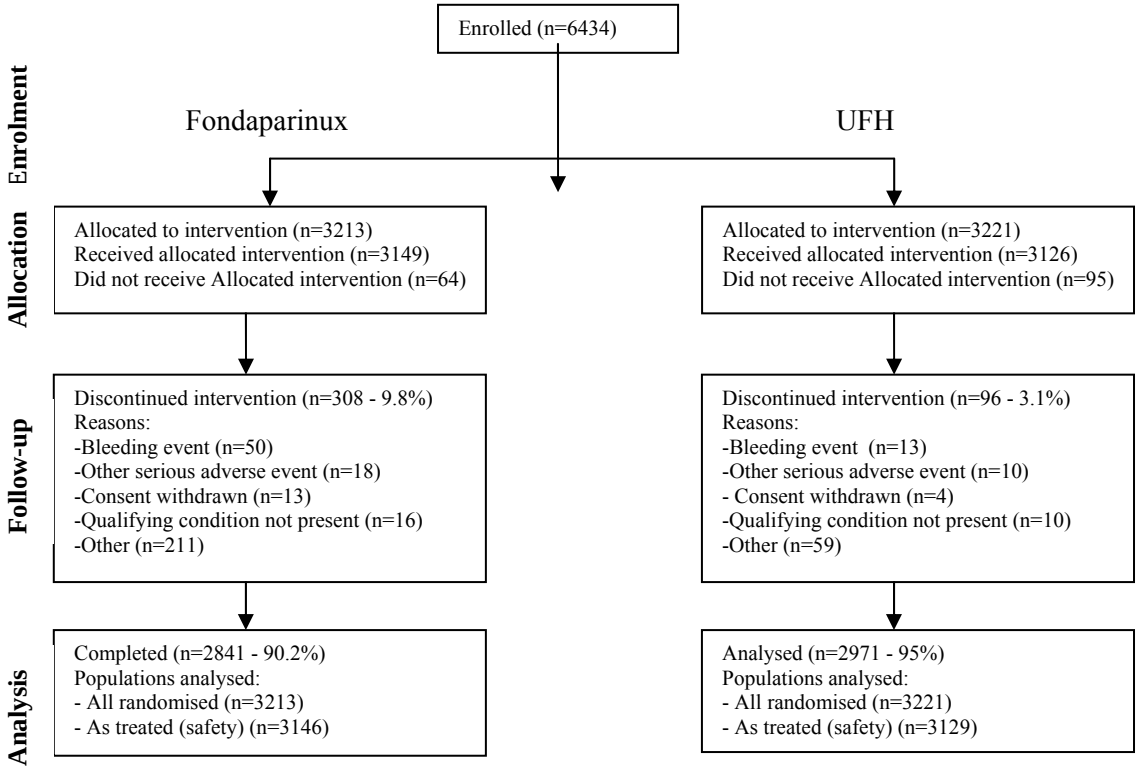
Results

The participant flow in OASIS-6 is shown below

STRATUM 1



STRATUM 2



There were 42 participating countries grouped into 4 distinct regions, with the Eastern European region randomising most of the subjects (47.5%). The top three recruiting countries were Russia, China, and India representing 16.7%, 12.4% and 11.7% of the overall population, respectively. Across

the 2 strata, more East European (43%) and Asian (40%) subjects were included in Stratum 1, while more East European (51.5%) and West European (23%) subjects were included in Stratum 2.

There were no notable differences in *baseline data* between the treatment groups in terms of demographic or clinical characteristics, or cardiovascular history, or time between onset of qualifying episode of chest pain/symptoms and randomisation. As in OASIS-5, the most frequently used medications during the initial hospitalisation period were ASA, beta-blockers, nitrates, statins, ACEi, and clopidogrel. The concomitant use of medications was similar between the groups within each study.

The summary of reperfusion strategies is shown in the table below.

Table 15. Summary of Actual Reperfusion Strategy for Index Event - All Randomised

	Overall		**Stratum 1**		**Stratum 2**	
n (%)	**Fond. N = 6036**	**Control N = 6056**	**Fond. N = 2823**	**Placebo N = 2835**	**Fond. N = 3213**	**UFH N = 3221**
Thrombolytic Agent						
No	3341 (55.4)	3314 (54.7)	630 (22.3)	613 (21.6)	2711 (84.4)	2701 (83.9)
Yes	2695 (44.6)	2742(45.3)	2193 (77.7)	2222 (78.4)	502 (15.6)	**520 (16.1)**
Fibrin Specific	425 (7.0)	443 (7.3)	8 (0.3)	8 (0.3)	417 (13.0)	435 (13.5)
Alteplase[1]	102 (24.0)	120 (27.1)	3 (37.5)	5 (62.5)	99 (23.7)	115 (26.4)
Reteplase[1]	141 (33.2)	119 (26.9)	2 (25.0)	0	139 (33.3)	119 (27.4)
Tenecteplase[1]	182 (42.8)	204 (46.0)	3 (37.5)	3 (37.5)	179 (42.9)	201 (46.2)
Non-Fibrin Specific	2267 (37.6)	2298 (37.9)	2183 (77.3)	2214 (78.1)	84 (2.6)	84 (2.6)
Streptokinase[1]	1950 (86.0)	1998 (86.9)	1890 (86.6)	1940 (87.6)	60 (71.4)	58 (69.0)
Urokinase[1]	317 (14.0)	300 (13.1)	293 (13.4)	274 (12.4)	24 (28.6)	26 (31.0)
Other[1]	3 (<0.1)	1 (<0.1)	2 (<0.1)	0	1 (<0.1)	1 (<0.1)
Primary PCI						
No	4147 (68.7)	4147 (68.5)	2813 (99.6)	2828 (99.8)	1334 (41.5)	1319 (41.0)
Yes	1889 **(31.3)**	1909 **(31.5)**	10 (0.4)	7 (0.2)	1879 (58.5)	1902 (59.0)
No Thrombolytic or PCI	1452 (24.1)	1405 (23.2)	620 (22.0)	606 (21.4)	832 (25.9)	799 (24.8)

1. The percentage of subjects receiving each thrombolytic agent is based on the total for fibrin-specific or non-fibrin specific totals.

The long-term use of agents and interventions that improve morbidity outcomes was balanced between treatment groups and the percentages of subjects who underwent PCI or CABG surgery at the follow-up visits were similar in both studies. Approximately 45% of subjects underwent thrombolysis, and 31% primary PCI as the initial reperfusion strategy for the index event, while 24% of subjects did not undergo any initial reperfusion.

Relevance of the OASIS-6 population to EU clinical practice

This was one of the main points discussed by the CHMP. The MAH was asked to clarify if the OASIS 6 study population could be considered as representative of the target population, taking current treatment practice and guideline recommendations into account. For example, only 53% of the included patients were allocated to UFH treatment while, according to European Heart Survey data, 85% of the target population is treated with UFH. The percentage of patients that underwent PCI, the best reperfusion strategy in STEMI according to guidelines, appears low compared to usual practice in Europe. In addition, a rather large proportion (84 %) of the studied patients undergoing thrombolysis were treated with non-fibrin-selective thrombolytics (mainly STK) and only 16% with fibrin-specific thrombolytics, which is not representative of current thrombolytic treatment, when mainly fibrin-specific thrombolytics are used. Moreover, the surprisingly high mortality rate observed in this study raised further concern regarding the possible differences in background therapy and treatment care as compared to current treatment practices in the Western population.

Further to a request from CHMP the Applicant submitted a thorough investigation of contemporary European registries (notably ACS-II and GRACE). According to the Applicant, the population in OASIS-6 trial is consistent with such registries (patient characteristics, use of concomitant therapies and mortality rates were comparable) and the use of reperfusion therapy reflects ESC recommendations. The company is of the opinion that non-fibrin specific thrombolytics are still

widely used in Europe, especially Eastern Europe and the UK. In OASIS-6 the use of non-fibrin specific thrombolytics varied across the European Union and was consistent with country specific data. Also the UFH use in OASIS-6 is consistent with ESC guideline recommendations.

The CHMP put this question to the SAG CVS, who acknowledged the differences between the OASIS-6 population and the populations included in the registries but also pointed out that registry data are populated to a large extent by active, highly motivated large centres with facilities for primary PCI in STEMI patients. Thus, despite the increasing availability of primary PCI, the majority of patients with STEMI in EU are still treated with thrombolytic therapy. It was stated that STK is still used in many European countries (Eastern Europe, UK) although the precise rates of non-fibrin specific and fibrin-specific thrombolytics prescribed in Europe are uncertain since current European registries and studies might not accurately reflect usual practice in Europe which is probably fairly heterogeneous. Moreover, it was suggested that too much attention should not be paid to the type of thrombolytic therapy often used in EU, as the pathophysiological mechanism is similar irrespective of the type of the thrombolytic agent.

Although firm evidence-based conclusions are not possible in this area, the SAG concluded that despite the population of patients included in OASIS-6 (notably in Stratum 1) not being fully representative of the target population, the study results could still be applicable to European patients.

Results of the primary endpoint

Fondaparinux demonstrated a clinically relevant and statistically significant 14% risk reduction relative to control in the primary endpoint (HR 0.86, 95% CI: 0.77, 0.96; p=0.008) in the overall randomised population, as shown below.

Table 16 Proportional Hazards Analysis of the First Occurrence of Adjudicated Death or Re-MI at Day 30 -

	Overall		**Stratum 1**		**Stratum 2**	
	Fond. N = 6036	**Control N = 6056**	**Fond. N = 2823**	**Placebo N = 2835**	**Fond. N = 3213**	**UFH N = 3221**
Events, n (%)	584 (9.7%)	675 (11.1%)	318 (11.3)	396 (14.0)	266 (8.3)	279 (8.7)
Adjusted Hazard Ratio (HR) (Fond. Vs control)	0.86		0.80		0.94	
95% CI	(0.77, 0.96)		(0.69, 0.93)		(0.79, 1.11)	
Adjusted HR p-value	0.008		0.003		0.460	

Consistent with the result in the overall randomised population, fondaparinux was superior to placebo in Stratum 1 (UFH not indicated) in the prevention of death or re-MI with a 20% risk reduction at Day 30 [HR 0.80; 95% CI: 0.069, 0.93; p=0.003). However, fondaparinux failed to demonstrate superiority over UFH (stratum 2). The interaction test between treatment and strata was not significant (p=0.11), indicating that the results of both strata were consistent with the overall results.

The results of adjudicated death or Re-MI at different time points are shown below.

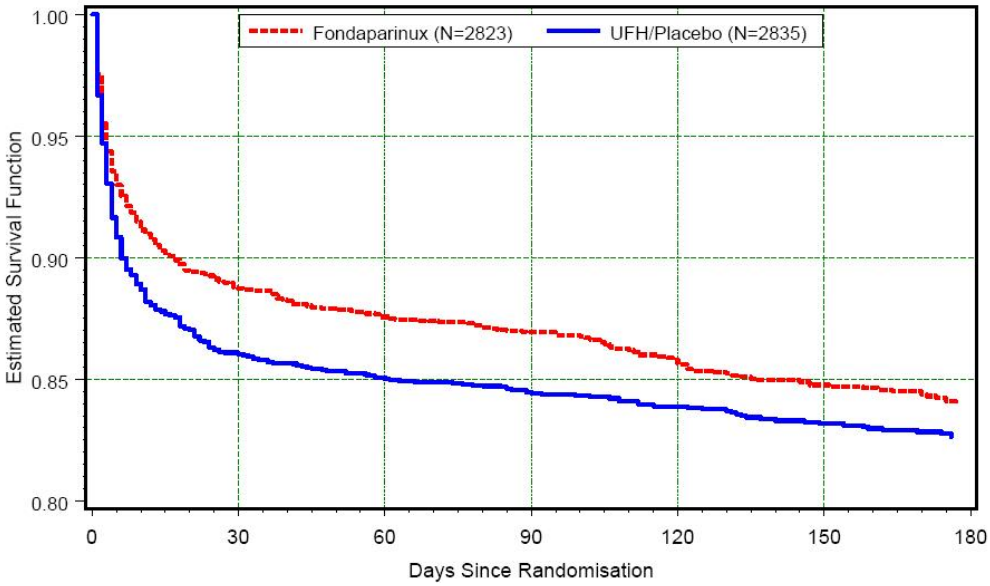
Table 17. Summary of the Proportional Hazards Analysis of Adjudicated Death or Re-MI at All Time points

Death/reMI Timepoint, n(%)	**Fondaparinux**	**Control**	**HR (95% CI)**	**p-Value**
Overall	*N=6,036*	*N=6,056*		
Day 9	443 (7.3%)	536 (8.9%)	0.82 (0.73, 0.93)	0.003
Day 30	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96)	0.008
Day 90	683 (11.3%)	796 (13.1%)	0.85 (0.77, 0.94)	0.002
Day 180	756 (12.5%)	855 (14.1%)	0.88 (0.79, 0.97)	0.008
Stratum 1 (vs Placebo)	*N=2,823*	*N=2,835*		
Day 9	240 (8.5%)	314 (11.1%)	0.76 (0.64, 0.90)	0.001
Day 30	318 (11.3%)	396 (14.0%)	0.80 (0.69, 0.93)	0.003
Day 90	369 (13.1%)	453 (16.0%)	0.83 (0.72, 0.95)	0.008
Day 180	414 (14.7%)	469 (16.5%)	0.87 (0.77, 1.00)	0.046
Stratum 2 (vs UFH)	*N=3,213*	*N=3,221*		
Day 9	203 (6.3%)	222 (6.9%)	0.91 (0.75, 1.10)	0.330

Day 30	266 (8.3%)	279 (8.7%)	0.94 (0.79, 1.11)	0.460
Day 90	314 (9.8%)	355 (11.0%)	0.87 (0.75, 1.02)	0.077
Day 180	342 (10.6%)	386 (12.0%)	0.87 (0.75, 1.01)	0.069

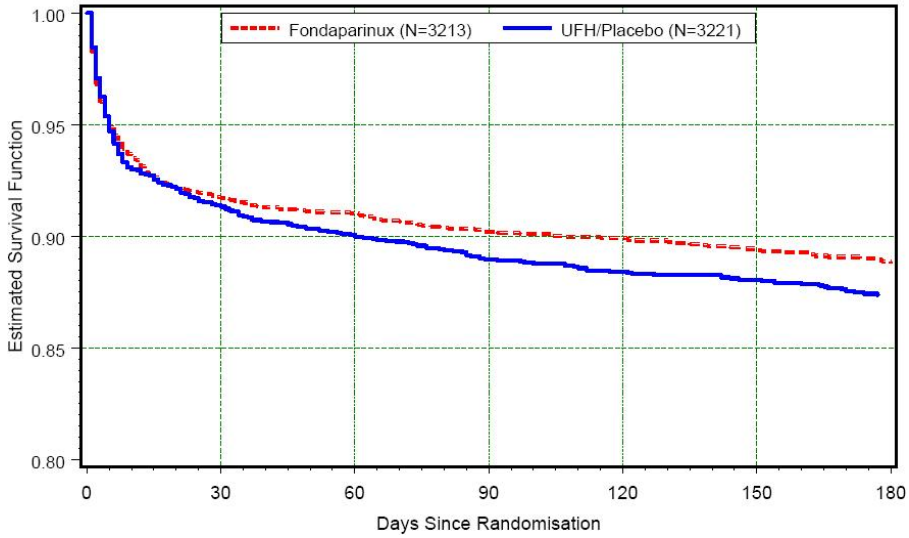
Fondaparinux was superior to placebo in reducing the risk of death and re-MI at all time points assessed, as by the hazard ratios and CIs and by the separation of Kaplan-Meier curves. The benefit of fondaparinux was observed at Day 9 with a significant 18% risk reduction and was sustained through Day 180 (risk reduction 12%). Again this overall risk reduction was significant in Stratum 1 but not in Stratum 2.

Figure 2 Kaplan-Meier Plot, Time to First Occurrence of Adjudicated Death or Re-MI, Stratum 1



The separation of the Kaplan-Meier curves showed a different profile in Stratum 2 relative to Stratum 1 (shown above). Event rates were generally lower than in Stratum 1 and there was very little separation of the survival curves until around Day 30, suggesting non-superiority to UFH up to that time. However, after Day 30, the curves separate showing a profile consistent with the overall results.

Figure 3 Kaplan-Meier Plot, Time to First Occurrence of Adjudicated Death or Re-MI, Stratum 2



The individual components of the primary endpoint (death and re-MI) at all time points are shown in the following tables.

Table 18 - Summary of the Proportional Hazards Analysis of **Adjudicated Death at All Time points**

Death **Timepoint, n(%)**	**Fondaparinux**	**Control**	**HR (95% CI)**	**p-Value**
Overall	*N=6036*	*N=6056*		
Day 9	368 (6.1%)	426 (7.0%)	0.86 (0.75, 0.99)	0.039
Day 30	470 (7.8%)	541 (8.9%)	0.87 (0.77, 0.98)	0.023
Day 90	545 (9.0%)	634 (10.5%)	0.86 (0.76, 0.96)	0.008
Day 180	599 (9.9%)	675 (11.1%)	0.88 (0.79, 0.99)	0.027
Stratum 1 (vs Placebo)	*N=2823*	*N=2835*		
Day 9	202 (7.2%)	252 (8.9%)	0.80 (0.66, 0.96)	0.018
Day 30	257 (9.1%)	321 (11.3%)	0.80 (0.68, 0.94)	0.008
Day 90	301 (10.7%)	354 (12.5%)	0.85 (0.73, 0.99)	0.037
Day 180	336 (11.9%)	375 (13.2%)	0.89 (0.77, 1.04)	0.135
Stratum 2 (vs UFH)	*N=3213*	*N=3221*		
Day 9	166 (5.2%)	174 (5.4%)	0.95 (0.77, 1.17)	0.623
Day 30	213 (6.6%)	220 (6.8%)	0.95 (0.79, 1.15)	0.631
Day 90	244 (7.6%)	280 (8.7%)	0.86 (0.72, 1.02)	0.087
Day 180	263 (8.2%)	300 (9.3%)	0.87 (0.73, 1.02)	0.088

In the overall "All Randomised Population", there was a reduction in the risk of death favouring fondaparinux, seen early at Day 9 with a clinically and statistically significant 14% reduction in risk and sustained through to Day 180 (12% risk reduction). Stratum 1 results support the conclusion that fondaparinux was superior to placebo in reducing the risk of death, as early as Day 9 with a statistically significant 20% risk reduction and was sustained through Day 90 (15% risk reduction). Although the results at Day 180 failed to achieve statistical significance, the hazard ratio remains consistent with the overall result for this endpoint. In Stratum 2, the event rates were generally lower than in Stratum 1, with non-superiority of the efficacy of UFH up to Day 30. However, after Day 30 the results in Startum 2 are consistent with the overall results.

Table 19 - Summary of the Proportional Hazards Analysis of **Adjudicated ReMI** at All Time points

Recurrent MI **Time point, n(%)**	**Fondaparinux**	**Control**	**HR (95% CI)**	**p-Value**
Overall	*N=6036*	*N=6056*		
Day 9	91 (1.5%)	134 (2.2%)	0.68 (0.52, 0.88)	0.004
Day 30	141 (2.3%)	172 (2.8%)	0.81 (0.65, 1.02);	0.069
Day 90	174 (2.9%)	217 (3.6%)	0.79 (0.65, 0.97);	0.023
Day 180	199 (3.3%)	242 (4.0%)	0.81 (0.67, 0.98);	0.031
Stratum 1 (vs Placebo)	*N=2823*	*N=2835*		
Day 9	49 (1.7%)	72 (2.5%)	0.67 (0.47, 0.97);	0.032
Day 30	74 (2.6%)	92 (3.2%)	0.79 (0.58, 1.07);	0.133
Day 90	88 (3.1%)	109 (3.8%)	0.79 (0.60, 1.05);	0.104
Day 180	101 (3.6%)	117 (4.1%)	0.85 (0.65, 1.10);	0.221
Stratum 2 (vs UFH)	*N=3213*	*N=3221*		
Day 9	42 (1.3%)	62 (1.9%)	0.68 (0.46, 1.01)	0.053
Day 30	67 (2.1%)	80 (2.5%)	0.83 (0.60, 1.15)	0.253
Day 90	86 (2.7%)	108 (3.4%)	0.79 (0.59, 1.04)	0.097
Day 180	98 (3.1%)	125 (3.9%)	0.77 (0.59, 1.01)	0.058

Similarly favourable results for fondaparinux were observed in the reduction in the risk of re-MI, with a clinically and statistically significant 32% reduction in risk at Day 9 in the overall population and sustained through to Day 180 (19%). The results in Stratum 1 and Stratum 2 were consistent with the the overall results but were only significant at Day 9 in Stratum 1.

Other efficacy outcomes by strata: stroke, severe ischemia and composite of Death/Re-MI/RI

The results for the composite of Death/re-MI/RI were significantly in favour of fondaparinux in stratum 1 and there was a favourable trend in stratum 2, which did not reach statistical significance.

Table 20. Summary of the Proportional Hazards Analysis of **Adjudicated Death/Re-MI/RI at All Time points** by Strata

Death/ReMI/RI				
Time point, n(%)	**Fondaparinux**	**Control**	**HR (95% CI)**	**p-Value**
Stratum 1 (vs Placebo)	**N=2823**	**N=2835**		
Day 9	253 (9.0%)	314 (11.1%)	0.77 (0.65, 0.91)	0.002
Day 30	332 (11.8%)	396 (14.0%)	0.81 (0.70, 0.94)	0.004
Day 90	383 (13.6%)	453 (16.0%)	0.84 (0.73, 0.96)	0.011
Day 180	427 (15.1%)	469 (16.5%)	0.88 (0.77, 1.00)	0.053
Stratum 2 (vs UFH)	**N=3213**	**N=3221**		
Day 9	213 (6.6%)	222 (6.9%)	0.91 (0.76, 1.10)	0.320
Day 30	278 (8.7%)	279 (8.7%)	0.94 (0.80, 1.11)	0.447
Day 90	328 (10.2%)	355 (11.0%)	0.88 (0.76, 1.02)	0.091
Day 180	357 (11.1%)	386 (12.0%)	0.88 (0.76, 1.02)	0.081

The the occurrence of stroke was low in the overall population. In Stratum 1, contrary to Stratum 2, there was a suggestion of treatment effect favouring fondaparinux over placebo which was most apparent at early time points; however in both Strata, the 95% CIs were wide and thus the results are inconclusive.

Table 21. Summary of the Proportional Hazards Analysis of **Adjudicated Stroke at All Time points** by Strata

Stroke				
Time point, n(%)	**Fondaparinux**	**Control**	**HR (95% CI)**	**p-Value**
Stratum 1 (vs Placebo)	**N=2823**	**N=2835**		
Day 9	16 (0.6%)	29 (1.0%)	0.55 (0.30, 1.01)	0.053
Day 30	24 (0.9%)	36 (1.3%)	0.66 (0.39, 1.10)	0.112
Day 90	32 (1.1%)	39 (1.4%)	0.81 (0.52, 1.29)	0.372
Day 180	34 (1.2%)	42 (1.5%)	0.80 (0.51, 1.25)	0.327
Stratum 2 (vs UFH)	**N=3213**	**N=3221**		
Day 9	29 (0.9%)	27 (0.8%)	1.04 (0.61, 1.77)	0.876
Day 30	43 (1.1%)	32 (1.0%)	1.04 (0.64, 1.69)	0.886
Day 90	49 (1.5%)	38 (1.2%)	**1.27** (0.83, 1.94)	0.277
Day 180	51 (1.6%)	47 (1.5%)	1.07 (0.72, 1.59)	0.755

Regarding severe ischemia, consistent with the overall population, fondaparinux was associated with statistically non-significant reductions in both Stratum 1 and Stratum 2 in the risk of severe ischemia.

Sub groups analyses, including PCI

Subgroup analyses on the primary outcome were performed according to the usual *demographic characteristics*. The results were consistent across various subgroups (age, sex, BMI, Creatinine Clearance) and no significant interactions were found, although results tended to vary slightly by country group, with higher event rates in Asia and lower in Western Europe, again opening the debate on the representativeness of the trial population.

Analysis of the primary outcome by prior use and concomitant anticoagulant treatment, by initial reperfusion strategy and by revascularisation procedure (PCI) were also performed. The relative effect of fondaparinux to control on death/re-MI at Day 30 was consistent among subjects who received thrombolysis or no initial reperfusion, as well as in those who received non-fibrin specific thrombolytics. In subjects receiving fibrin specific thrombolytics the rates of death/re-MI were similar.

However, among subjects who underwent primary PCI for the index event, fondaparinux did not provide any benefit at Day 30 compared to control.

Table 22. Proportional Hazards Analysis of Time to First Occurrence of the primary endpoint by Initial Reperfusion Strategy

Covariate Endpoint/Timepoint	No. Events/No. Analysed (%)		HR (95% CI)[1]	Treatment by covariate interaction p-value
	Fondaparinux	Control		
Adjusting for Reperfusion Strategy	584/6036 (9.7)	675/6056 (11.1)	0.89 (0.78, 1.02)	0.002
No reperfusion	176/1452 (12.1)	211/1405 (15.0)	0.79 (0.65, 0.97)	
Thrombolytic Agent	295/2695 (10.9)	373/2742 (13.6)	0.79 (0.68, 0.93)	
Primary PCI	113/1889 (6.0)	91/1909 (4.8)	1.26 (0.96, 1.66)	
Thrombolytic Use				
Non-fibrin specific agent	244/2267 (10.8)	318/2298 (13.8)	0.77 (0.65, 0.90)	
Fibrin specific agent	50/425 (11.8)	54/443 (12.2)	0.98 (0.67, 1.44)	
Not undergoing primary PCI	471/4147 (11.4)	584/4147 (14.1)	0.80 (0.70, 0.90)	Not done
Stratum 1	318/2813 (11.3)	395/2828 (14.0)	0.80 (0.69, 0.92)	
Stratum 2	153/1334 (11.5)	189/1319 (14.3)	0.79 (0.64, 0.98)	

[1]Hazard ratio, 95% CI and p-values are adjusted for strata and the covariate of interest.

When analysed according to non-primary PCI, fondaparinux did not provide any benefit at Day 30 compared to control either, as shown in the table below.

Table 23 Proportional Hazards Analysis of the primary endpoint by PCI or CABG (post-initial reperfusion)

Covariate Endpoint/Timepoint	No. Events/No. Analysed (%)		HR (95% CI)[1]	Treatment by Covariate Interaction p value
	Fondaparinux	Control		
PCI (excluding primary PCI)				
Overall	584/6034 (9.7)	675/6051 (11.2)	0.86 (0.77, 0.96)[1]	0.228
No	564/5857 (9.6)	658/5864 (11.2)	0.85 (0.76, 0.95)	
Yes	20/177 (11.3)	17/187 (9.1)	1.27 (0.67, 2.43)	
CABG				
Overall	584/6034 (9.7)	675/6051 (11.2)	0.86 (0.77, 0.96)[1]	0.709
No	579/5962 (9.7)	668/5981 (11.2)	0.86 (0.77, 0.96)	
Yes	5/72 (6.9)	7/70 (10.0)	0.69 (0.22, 2.19)	

1. Adjusted hazard ratio

Safety

A total of 12,092 patients were randomised; 5,658 were allocated to Stratum 1 (2823 fondaparinux and 2835 placebo) and 6,434 were allocated to Stratum 2 (3213 fondaparinux and 3221 enoxaparin).

Table 24: Summary of treatment completion status and reasons for withdrawal

n (%)	Stratum 1		Stratum 2	
	Fondaparinux N=2823	Placebo N=2835	Fondaparinux N=3213	UFH N=3221
Not Treated	19 (0.7)	13 (0.5)	64 (2.0)	95 (2.9)
Treated	2804 (99.3)	2822 (99.5)	3149 (98.0)	3126 (97.1)
Completion Status of Treated Subjects				
Completed study drug	2614 (93.2)	2639 (93.5)	2841 (90.2)	2971 (95.0)
Early Permanent discontinuation	189 (6.7)	183 (6.5)	308 (9.8)	96 (3.1)
Missing	1 (<0.1)	0	0	59 (1.9)
Reason for Early Permanent Discontinuation	N=2823	N=2835	N=3213	N=3126
Bleeding Event	33 (1.2)	25 (0.9)	50 (1.6)	13 (0.4)
Other Serious Adverse Event	12 (0.4)	17 (0.6)	18 (0.6)	10 (0.3)
Consent withdrawn	12 (0.4)	15 (0.5)	13 (0.4)	4 (0.1)
Qualifying condition not present	13 (0.5)	6 (0.2)	16 (0.5)	10 (0.3)
Other	119 (4.2)	120 (4.2)	211 (6.6)	59 (1.9)

Discontinuation rates were similar in stratum 1. However, in stratum 2, discontinuation in the fondaparinux group was 3-fold more frequent than in UFH. This is attributed to the different durations of therapy of fondaparinux (up to 8 days) compared to UFH (up to 48 hours maximum).

Bleeding Events

No statistically significant difference in the incidence of *adjudicated severe haemorrhage* was observed between fondaparinux and placebo/UFH in the overall population, although the values for fondaparinux were lower at all time points. In stratum 1, the incidence was statistically lower in fondaparinux at day 9 and day 30, but no statistically significant difference was observed during the on-therapy period. In stratum 2, the incidence during the on-therapy period was similar in fondaparinux and UFH groups (1% vs 1.2%). Similar trends were observed at the different endpoints analysis (see table 11).

Table 25 Summary of time to first occurrence of adjudicated severe haemorrhage during on-therapy period, days 9, 30, 90 and 180.

	Overall		Stratum 1		Stratum 2	
	Fondaparinux (N=5954)	Control (N=5947)	Fondaparinux (N=2808)	Placebo (N=2818)	Fondaparinux (N=3146)	UFH (N=3129)
On-Therapy						
Number of Events, n (%)	61 (1.0)	77 (1.3)	29 (1.0)	41 (1.5)	32 (1.0)	36 (1.2)
Hazard Ratio	0.79		0.70		0.88	
95% CI, p-value	(0.56, 1.10), 0.166		(0.44, 1.13), 0.148		(0.54, 1.40), 0.614	
Day 9						
Number of Events, n (%)	64 (1.1)	83 (1.4)	28 (1.0)	46 (1.6)	36 (1.1)	37 (1.2)
Hazard Ratio	0.77		0.61		0.97	
95% CI, p-value	(0.55, 1.06), 0.111		(0.38, 0.97), 0.036		(0.61, 1.53), 0.890	
Day 30						
Number with Event	72 (1.2)	93 (1.6)	31 (1.1)	49 (1.7)	41 (1.3)	43 (1.4)
Hazard Ratio	0.77		0.63		0.95	
95% CI, p-value	(0.57, 1.05), 0.095		(0.40, 0.99), 0.043		(0.62, 1.45), 0.808	
Day 90						
Number with Event	82 (1.4)	107 (1.8)	34 (1.2)	52 (1.8)	48 (1.5)	55 (1.8)
Hazard Ratio	0.76		0.65		0.87	
95% CI, p-value	(0.57, 1.01), 0.062		(0.42, 1.00), 0.050		(0.59, 1.28), 0.468	
Day 180						
Number with Event	89 (1.5)	110 (1.8)	38 (1.4)	53 (1.9)	51 (1.6)	57 (1.8)
Hazard Ratio	0.80		0.71		0.89	
95% CI, p-value	(0.61, 1.06), 0.122		(0.47, 1.08), 0.108		(0.61, 1.29), 0.535	

Regarding *major bleeding* (see table **), there was a lower incidence in stratum 1 in the fondaparinux group compared to placebo group. This difference did not meet statistical significance during the on-therapy period, but was statistically significant at day 30 and bordering significance at day 9. Further to a request from CHMP, the MAH attempted to explain this surprising finding, for which there is no clear explanation. It is plausible that the better efficacy observed with fondaparinux relative to placebo, might have resulted in fewer interventions (PCI, CABG, GPIIb/IIIa inhibitor, need for open-label anticoagulant), and as a consequence lower bleeding rates. Interestingly, when the components of severe haemorrhage or major bleeding are examined, the lower risk seen in fondaparinux patients is most evident for events of fatal bleeding (1.1% vs. 0.7%) and cardiac tamponade (1.1% vs. 0.5%).

No difference between treatment groups was observed in stratum 2.

Table 26 Summary of time to first occurrence of adjudicated of major haemorrhage during the on-therapy period and at days 30, 90, 180-As treated population.

	Overall		Stratum 1		Stratum 2	
Major Bleed	Fondaparinux (N=5954)	Control (N=5947)	Fondaparinux (N=2808)	Placebo (N=2818)	Fondaparinux (N=3146)	UFH (N=3129)
On-Therapy[1], n (%)						
Number with Major Bleed	99 (1.7)	120 (2.0)	40 (1.4)	53 (1.9)	59 (1.9)	67 (2.1)
Hazard Ratio	0.82		0.75		0.88	
95% CI, p-value	(0.63, 1.07), 0.146		(0.50, 1.13), 0.170		(0.62, 1,24), 0.459	
Day 9, n (%)						
Number with Major Bleed	104 (1.7)	128 (2.1)	39 (1.4)	58 (2.1)	65 (2.1)	70 (2.2)
Hazard Ratio	0.81		0.67		0.92	
95% CI, p-value	(0.62, 1.05), 0.107		(0.45, 1.00), 0.052		(0.66, 129), 0.645	
Day 30, n (%)						
Number with Major Bleed	118 (2.0)	142 (2.4)	44 (1.6)	65 (2.3)	74 (2.4)	77 (2.5)
Hazard Ratio	0.83		0.67		0.96	
95% CI, p-value	(0.65, 1.05), 0.124		(0.46, 0.98), 0.041		(0.69, 1.31), 0.780	

Of note, the incidences of major bleeding in fondaparinux subjects were somewhat higher in Stratum 2 compared to Stratum 1 at all time points for both the All Randomized (data not show) and As Treated populations. The explanation for this is not entirely clear but may be a reflection of the slightly different levels of use of concomitant therapies and interventions which may contribute to the background bleeding risk in the two strata.

There were no major differences between treatment groups in minor bleeding or minor haemorrhage, or in the type of bleeding or bleeding event.

Post-Hoc Analysis in PCI patients

A total of 3715 patients (1862 in fondaparinux and 1853 in control group) underwent a primary PCI and 444 (229 fondaparinux and 215 control group) a non-primary PCI. Several post-hoc analyses of the subgroup of patients undergoing PCI during the treatment period were carried out regarding clinical outcome, bleeding events and complications.

As in OASIS 5, an unexpected AE related to catheter thrombus was reported in OASIS 6. A total of 34 possible "catheter thrombus" were identified, of which 4 were excluded (2 occurred during angiography, and 2 were incorrectly coded). Of the remaining 30 events, 23 were adjudicated and all occurred in fondaparinux group; 22 during primary PCI and only 1 during non-primary PCI.

- Primary PCI

Events in patients undergoing primary PCI during initial hospitalisation and within 8 days of randomisation and who had received at least 1 dose of study drug prior to the procedure were analysed.

Table 27 Complications during primary PCI.

	Fondaparinux (N=1862)	UFH/Control (N=1853)
Total No. of PCI's performed	1862 (100.0)	1855 (100.0)
Vascular site complications during PCI		
Vascular site complications overall	31 (1.7)	36 (1.9)
Pseudoaneurysm requiring closure	9 (0.5)	3 (0.2)
Large hematoma	11 (0.6)	25 (1.3)
AV fistula	7 (0.4)	1 (<0.1)
Other vascular site complications	4 (0.2)	7 (0.4)
Other (i.e. coronary) complications during PCI		
Coronary complications overall	208 (11.2)	159 (8.6)
Abrupt closure of coronary artery	14 (0.8)	5 (0.3)
New angiographic thrombus	55 (3.0)	26 (1.4)
Investigator reported catheter thrombus[1]	28 (1.5)	1 (<0.1)
Catheter thrombus confirmed by adjudication[2]	22 (1.2)	0
No-reflow phenomenon	58 (3.1)	50 (2.7)
Dissection with reduced flow	14 (0.8)	15 (0.8)
Perforation	3 (0.2)	1 (<0.1)
Other complications	71 (3.8)	65 (3.5)
Clinical events during PCI		
Death	12 (0.6)	13 (0.7)
MI	0	1 (<0.1)
Stroke	2 (0.1)	3 (0.2)
Other Clinical Event	23 (1.2)	22 (1.2)

Stroke, death and MI occurred with a low incidence in both treatment groups.

Vascular site complications were also reported with a low incidence in both treatment groups (1.7% in fondaparinux vs 1.9% in UFH), although in line with the results in OASIS-5, large haematomas were twice as frequent in UFH (1.3%) compared to fondaparinux group (0.6%).

As observed in OASIS-5, the most frequent complications in the fondaparinux group compared to UFH were related to coronary complications (11.2% vs 8.6%). They included new angiographic thrombus and abrupt closure of coronary artery, followed by investigator-reported and adjudicated catheter thrombus (reported in 22 patients compared to none in UFH group; 1 patient died during the procedure - he developed a cardiogenic shock and received open label UFH and subsequently died). Of the 22 cases, 2 patients received open label UFH prior to the procedure, 19 did not received open label UFH and in one case it is unknown. It should be noted that 14 of 19 cases received UFH during the procedure due to the catheter thrombus events.

Use of UFH during primary PCI

The absence of catheter thrombus in UFH patients undergoing a primary PCI, suggests that catheter thrombus risk was negligible when UFH is used as adjunct during PCI. Consequently, the Applicant has further analysed patients receiving open-label UFH.

In fondaparinux patients undergoing a primary PCI, the use of UFH was on background of i.v. fondaparinux administered immediately prior to the procedure. In the non-primary PCI patients, the use of UFH was on the background of fondaparinux administered s.c. prior to the procedure.

In patients undergoing primary PCI, a total of 689 received open-label UFH before or before/during the procedure, of which a similar proportion of patients in both groups had received UFH (12.5% in fondaparinux and 12.3% in the control group). However, a higher proportion of patients in fondaparinux group (9%) received UFH during the procedure compared to the control group (5.7%). Additionally, the median dose of UFH administered before or before/during PCI was similar in both groups. However, during the procedure, the median dose of UFH administered to fondaparinux patients was higher than that administered in the control group (see table 17).

Table 28 Summary of subjects undergoing Primary PCI receiving open-label UFH as adjunct to the procedure

	Fondaparinux (N=1862)	Control (N=1853)
Total No. of PCI Performed	1862	1855
UFH Before PCI, n (%)	233 (12.5)	228 (12.3)
Median Dose [IU] (Range)	5000 (175-10300)	5000 (100-50000)
UFH During PCI, n (%)	167 (9.0)	105 (5.7)
Median Dose [IU] (Range)	4000 (40-26000)	3000 (100-13000)
UFH Before and/or During PCI, n (%)	374 (20.1)	315 (17.0)
Median Dose [IU] (Range)	5000 (120-26000)	5000 (200-50000)

2. Safety outcomes in patients undergoing primary PCI

Adjudicated severe haemorrhage was approximately twice more frequent in fondaparinux group compared to the control group on-therapy (0.8% vs 0.4%) and at day 9 (0.9% vs 0.5%). Major bleeding rates were similar on therapy in both fondaparinux and control group (1.8% vs 1.6%) and slightly higher in fondaparinux at day 9 (2% vs 1.6%).

SAEs occurring post-PCI and up to day 9 were also slightly increased in fondaparinux (4.8%) compared to control group (3.9%).

In the subgroup of patients receiving adjunct UFH, the bleeding outcomes were similar in both groups: major bleeds on-therapy (1.3% vs 1.6% in fondaparinux and control) and at day 9 (1.6% in both groups), and slightly increased regarding severe haemorrhage on therapy (0.8% vs 0.6% in fondaparinux and control) and at day 9 (1.1% vs 0.6%, respectively).

There was no benefit in reducing the risk of death and death/recurrent MI taken together at day 30 in fondaparinux patients compared to the control group (death/re-MI : 6.1% vs 5.1%; death : 4.5% vs 3.9%; Re-MI : 1.9% vs 1.5% in fondaparinux and control respectively). See table 18

Table 29 Number and percent of patients receiving study drug prior to primary PCI, experiencing adjudicated events post-PCI up to day 30

	Fondaparinux (N=1862)	Control (N=1853)
Total No. of PCIs Performed	1862	1855
Death/Re-MI	114 (6.1)	94 (5.1)
Death	84 (4.5)	73 (3.9)
Re-MI	36 (1.9)	27 (1.5)

In the sub-group of patients receiving adjunct UFH, the rate of death/Re-MI taken together was slightly increased in fondaparinux (4.8%) than in the control group (4.1%), as well as rate of death (3.7% vs 3.2% in fondaparinux and control respectively). Re-MI taken separately was reported in a similar rate in both groups (1.2% in fondaparinux and 1.3% in control group).

Table 30 Number and percent of patients receiving study drug prior to primary PCI, experiencing adjudicated events post-PCI up to day 30 with adjunct UFH therapy

	Fondaparinux	Control
Procedures with Adjunct UFH[1]	374	315
Adjudicated Event[2]		
Death/Re-MI	18 (4.8)	13 (4.1)
Death	14 (3.7)	10 (3.2)
Re-MI	4 (1.2)	4 (1.3)

- **Non-primary-PCI**

A total of 444 patients (229 in fondaparinux and 215 in the control group) underwent 639 non-primary PCI (318 in fondaparinux and 321 in the control group), defined as any PCI other than primary PCI that occurred after randomisation in any stratum and at any time during the study period. The most common reason for the procedure was routine practice (approximately 55% in both groups), however non-primary PCI due to refractory PCI was more frequent in fondaparinux than in the control group (11% vs 8% respectively) as well as for rescue for failed thrombolysis (18.2% vs 13.4%).

Coronary complications (7.2% fondaparinux vs. 5.9% control) were most frequent complication observed during the non-primary-PCI. One patient experienced an adjudicated catheter thrombus in fondaparinux group. This patient did not receive open-label-UFH prior the procedure but received UFH during the procedure due catheter thrombus. The patient recovered with no ischemic events. As addressed above, no catheter thrombus events were reported in UFH Group. The other coronary complications were similar in both treatment groups.

Vascular site complications were also more frequent in fondaparinux group than in the control group (2.8% vs 1.6%), with the most frequents events represented by haematoma (2.2% vs 0.9%).

Death was similar in both treatment groups (0.3%) and MI occurred in one fondaparinux patient.

Use of UFH during non-primary PCI

As addressed above in the primary PCI analysis, the use of UFH was on the background of fondaparinux administered s.c. prior to the procedure in the non-primary PCI patients.

A total of 423 patients undergoing 462 non-primary-PCI procedures received UFH as an adjunct to the procedure. More patients received UFH before/during PCI in fondaparinux group (74.8%) compared to control group (69.8%); of which 34.6% (fondaparinux) and 31.5% (control) received UFH before PCI, and 46.2% compared to 43.3% during PCI.

2. Safety outcome

Mortality rate and re-MI, taken separately or together, from the day of PCI (including events occurring prior to PCI on the day that the procedure was conducted) up to day 30 were higher in fondaparinux group. Similar results were also observed in each stratum; in Stratum 1, death and death/Re-MI were approximately two times higher in fondaparinux patients than in the control group, whilst re-MI was similar in both treatment groups. In stratum 2, death, Re-MI and death/Re-MI were also more frequent with fondaparinux than in the control group, as shown in the table below.

Table 31: Number of patients experiencing adjudicated events from the Day on which non-primary PCI was conducted and up to day 30.

Overall Stratum	**Fondaparinux (N=229)**	**Control (N=215)**
No PCIs Performed	318	321
Death/Re-MI	24 (7.5)	14 (4.4)
Death	17 (5.3)	9 (2.8)
Re-MI	8 (2.5)	5 (1.6)
Stratum 1	**Fondaparinux (N=118)**	**UFH (N=106)**
No PCIs Performed	122	111
Death/Re-MI	14 (11.5)	8 (7.2)
Death	11 (9.0)	5 (4.5)
Re-MI	3 (2.5)	3 (2.7)
Stratum 2	**Fondaparinux (N=111)**	**Placebo (N=109)**
No PCIs Performed	196	210
Death/Re-MI	10 (5.1)	6 (2.9)
Death	6 (3.1)	4 (1.9)
Re-MI	5 (2.6)	2 (1.0)

In the subgroup of patients receiving adjunct UFH, death was reported in a similar rate in both groups however, Re-MI and death/Re-MI were approximately twice as frequent in fondaparinux patients as in the control group.

Table 32 Number of patients with adjunct UFH experiencing adjudicated events from the Day on which non-primary PCI was conducted and up to day 30.

	Fondaparinux (N=229)	Control (N=215)
Total No of PCIs With Adjunct UFH[1]	238	224
Adjudicated Event		
Death/Re-MI	25 (10.5)	15 (6.7)
Death	9 (3.8)	8 (3.6)
Re-MI	16 (6.7)	8 (3.6)

Severe haemorrhage was more frequent in fondaparinux on therapy (1.5% vs. 0.6%) and at day 9 (1.9% vs 0.9%) compared to the control group. In the subgroup of patients who received adjunct UFH, severe haemorrhage occurred in a similar frequency in both groups of therapy (0.8% fondaparinux and 0.9% control) and at day 9 (1.7% and 1.3%, respectively). Major bleeds occurred with a similar frequency in both treatment groups. SAEs post-PCI and up to day 9 were more frequent in fondaparinux than in the control group (6.6% vs 3.7%). Of these, major bleeding were slightly more frequent in the control group than fondaparinux, on-therapy (2.2% vs 0.8% respectively) and at day 9 (2.7% vs 2.1%).

Common Adverse Events and Serious Adverse Events

The incidence of AEs in the overall population was similar in both treatment groups: 32% in fondaparinux and 33% in the control group (33% in fondaparinux vs. 34% in placebo and 32% in both fondaparinux and UFH). The most frequent AEs were assigned to "general disorders" and "cardiac" SOCs: pyrexia (3% in both groups), atrial fibrillation (3% vs. 2% in fondaparinux and control group, respectively), chest pain (1.8% vs. 1.3% respectively), headache (1.8% vs. 2% respectively), ventricular tachycardia (1.3% in both groups), hypotension (1.3% in both groups), vomiting (1% in both groups), haematoma (0.7% in both groups) and puncture site haemorrhage (0.2% in both groups). A similar trend was observed across the two strata.

On-therapy SAEs were equally reported in the two treatment groups: 3% of patients (1% were drug-related) in stratum 1 and 4% (1.5% were drug-related) in stratum 2. The most frequent SAEs were related to bleeding (e.g. digestive bleeding, coronary artery thrombosis, pericardial haemorrhage and cerebrovascular haemorrhage).

Regarding other events of special interest, 10 (0.16%) patients experienced thrombocytopenia in fondaparinux compared to 4 (0.06%) in the control groups up to and including day 30. It was more frequent in stratum 2 (9 [0.028%] in fondaparinux and 3 [0.09%] in UFH group) than in stratum 1 (1 in each treatment group). Only one patient (UFH group) experienced HIT.

Discussion

This new indication in ACS, with and without ST-segment elevation, is based on 2 large phase III pivotal studies (OASIS 5 in UA/NSTEMI and OASIS 6 in STEMI) and 4 phase II supportive trials.

The selection of the 2.5mg dose for the phase II programme might be considered surprising, as unlike LMWHs, where the higher VTE treatment doses are approved for use in UA/NSTEMI, it is the same fondaparinux dose used for the prevention of VTE. Despite the lack of a strong clinical rationale (other than safety considerations) to support the dose selection, the observed efficacy and safety profile of fondaparinux 2.5mg for the acute treatment of ACS raises the question whether the lower VTE prevention doses of the LMWHs might also be effective and better tolerated. However, unlike those conducted with fondaparinux, the phase II ACS studies for the LMWHs did not evaluate the wide dose range that included the lower VTE prevention doses.

Efficacy

The two pivotal trials supporting the indication of fondaparinux in ACS are methodologically sound, pragmatic in their design, and appear to be well conducted.

The primary *objective* in OASIS-6 was to evaluate whether fondaparinux was superior to a control reflecting a usual care (UFH or placebo) in preventing death or recurrent MI (re-MI) up to Day 30 in subjects presenting with STEMI. Fondaparinux demonstrated a clinically relevant and statistically significant 14% risk reduction relative to control in the primary endpoint in the overall randomised population. Consistent with this result, fondaparinux was superior to placebo in Stratum 1 (UFH not indicated) in the prevention of death or re-MI with a 20% risk reduction at Day 30. However, fondaparinux failed to demonstrate superiority over UFH (stratum 2). Fondaparinux also significantly reduced the of all cause mortality at Day 30; as with the primary endpoint, this finding was also significant in Stratum 1 but not in Stratum 2. Interaction tests between treatment and strata indicated that the results of both strata were consistent with the overall results.

These effects were consistent across pre-specified subgroups such as elderly, renally impaired patients and type of concomitant anti-platelet aggregant medication. Nevertheless, among subjects who underwent primary PCI for the index event, fondaparinux did not provide any benefit at Day 30 compared to control; in fact there was a trend observed in favour of the control group. Similar results were obtained when analysed according to non-primary PCI. When the primary PCI patients are excluded from the analysed population, the results of the primary endpoint are significantly in favour of fondaparinux therapy in the overall population and in both of the strata. Consequently, and especially in the light of the serious coronary complications observed in fondaparinux-treated patients during PCI in both OASIS trials (see discussion on Safety), the Applicant decided to apply for an indication in the treatment of STEMI in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy, thus excluding patients undergoing invasive management. The CHMP is in agreement, and the indication and trial results have been adequately reflected in sections 4.1 and 5.1 of the SPC, respectively.

The main issue regarding OASIS-6 discussed by the CHMP and referred to the SAG CVS was the relevance, with respect to current EU clinical practice, of the population studied in OASIS-6, particularly in terms of the low use of UFH, PCI and fibrin-specific thrombolytics, and the very high use of streptokinase [84% of patients treated with a thrombolytic were treated streptokinase] *(for a more detailed discussion, see page 26 of this report)*. Further to a request from CHMP the Applicant submitted a thorough investigation of contemporary European registries (notably ACS-II and GRACE). The SAG acknowledged notable differences between the OASIS-6 population and the populations included in the registries but also pointed out that registry data are populated to a large extent by active, highly motivated large centres with facilities for primary PCI in STEMI patients. Moreover, it was suggested that too much attention should not be paid to the type of thrombolytic therapy often used in EU, as the pathophysiological mechanism is similar irrespective of the type of the thrombolytic agent. Thus, although firm evidence-based conclusions are not possible in this area, the SAG concluded, and the CHMP agreed, that despite the population of patients included in OASIS-6 (notably in Stratum 1) not being fully representative of the target population, the study results were still applicable to European patients. Nonetheless, the percentage of patients undergoing primary PCI (31%) and treated with non-fibrin specific thrombolytics are reflected in section 5.1 of the SPC.

The main objective in OASIS-5 was to evaluate whether fondaparinux 2.5mg was “non-inferior”, or superior to, enoxaparin in preventing death and ischemic events (MI or RI) up to Day 9 in the acute treatment of subjects with UA/NSTEMI concurrently managed with standard medical therapy. Fondaparinux was non-inferior to enoxaparin in the early prevention of adjudicated death, MI or RI at Day 9. There was a tendency to a reduction in the risk of death, MI and RI with fondaparinux at day 14 which was sustained at days 30, 90 and 180. In addition, fondaparinux was associated with a significant reduction in all-cause mortality at Day 30. As in OASIS-6, these effects were consistent across pre-specified subgroups such as elderly, renally impaired patients and type of concomitant anti-platelet aggregant medication.

However, treatment with fondaparinux did not result in the reduction of ischaemic events or death in the PCI subgroup. Taking into account the higher incidence of serious coronary complications patients in both pivotal trials (see safety discussion later) coupled to the negative trends regarding efficacy observed in OASIS-6 in patients undergoing PCI, the CHMP debated at length the benefit:risk balance in this patient population. Further to a recommendation by the SAG CVS, endorsed by CHMP, the Applicant was asked to discuss a restriction to the use of fondaparinux in UA/STEMI patients for whom an early invasive management is not recommended. The Applicant argued in writing at an oral explanation that the diagnosis of NSTEMI can be problematic and the decision on whether to refer the patient for invasive treatment is often delayed whilst the patient is under observation and the results of numerous tests are waited. The decision-making algorithm for the management of NSTEMI patients in the new ESC treatment guidelines clearly defines the words "urgent" (i.e. < 2hours) and "early" (i.e. < 72 hours) in the context of invasive management strategies. Considering that prompt treatment is essential for patients presenting with a suspicion of UA or NSTEMI and should be administered as soon as the diagnosis is possible, but not necessarily confirmed, the Applicant believes that a restriction to "early" would mean that the majority of patients will not have the benefit of treatment with fondaparinux, since most patients will have started some other form of anticoagulation by then. Delaying treatment until a decision regarding invasive treatment is clearly not an option.

Thus, if treatment with fondaparinux were delayed for at least 72 hours, there would be very few patients to treat since the vast majority would already have received some other anticoagulation. Given that treatment with fondaparinux compared to enoxaparin was beneficial from a bleeding perspective (see discussion un Safety), equally effective and associated with a clear tendency for reduced mortality, the CHMP agree with the Applicant that the indication should be restricted to patients *patients for whom urgent (<120mins) invasive management (PCI) is not indicated*.

Safety

In OASIS-6, no statistically significant difference in the incidence of *adjudicated severe haemorrhage* was observed between fondaparinux and placebo/UFH in the overall population, although the values for fondaparinux were lower at all time points. In stratum 1, the incidence was statistically lower in fondaparinux at day 9 and day 30, but no statistically significant difference was observed during the on-therapy period. The results on severe haemorrhage were consistent across prespecified subgroups such as elderly, renally impaired patients and type of concomitant antiplatelet medications. However, in patients undergoing primary PCI, the incidence of severe haemorrhage was numerically higher with fondaparinux. Equally worrying was the noticeably higher incidence of serious coronary complications (including new angiographic thrombus, abrupt closure of coronary artery and catheter thrombus) observed in the fondaparinux group.

Treatment with fondaparinux in OASIS-5 resulted in a significant (48%) lower risk of major bleeding up to and including day 9 compared to treatment with enoxaparin. Other types of bleeds, including severe bleeding according to the TIMI criteria and minor bleeding, were also lower on fondaparinux. Of note, subjects who had a major or minor bleeding during hospitalisation had a significantly higher rate of death at day 30 than subjects without a bleeding event, regardless of treatment group. The Applicant has performed two *ad-hoc* analyses to assess the clinical implications of bleeding which appear to indicate that the difference in mortality between the treatment groups observed at the end of the study may be related to the lower rate of bleeding with fondaparinux *(for a more detailed discussion, see page 15 of this report)*.

Consistent with its lower bleeding risk in the overall population, in patients undergoing PCI fondaparinux was also associated with a significantly lower incidence of major bleeding. Worryingly however, and as observed in primary PCI patients in OASIS-6, coronary complications occurred more frequently with fondaparinux. In addition to the more frequent guiding catheter thrombus, more disturbing are the higher rates of coronary abrupt closure and new angiographic thrombus. The occurrence of catheter thrombus (unblinded), an unexpected AE during the course of the study, prompted an amendement of the study protocol to emphasis the correct administration of fondaparinux intravenously during the PCI and to reiterate that heparinised catheter flushes could be used.

Proposed management strategy for fondaparinux-treated patients undergoing PCI: Use of UFH
Acknowledging the complications in fondaparinux patients undergoing PCI observed in OASIS-5 and OASIS-6 and aware of the fact that UA/NSTEMI patients treated with fondaparinux may need to undergo PCI, the Applicant proposes in section 4.2 of the SPC that UFH be administered as an adjunct to the procedure (as per local practice), given that there were no instances of guiding catheter thrombus reported in patients managed following the above recommendation. This generated much debate at CHMP, as this proposed PCI management strategy has not been has not been formally studied in UA/NSTEMI patients. The Applicant argued that there are (limited) data showing the safety of this treatment combination; nonetheless the CHMP consider, and the SAG CVS agree, that the available evidence is insufficient and a Post-Authorisation Safety Study to evaluate the safety in fondaparinux-treated patients undergoing PCI receiving adjunctive therapy with one of two regimens of i.v. UFH (standard and reduced dose) as the PCI adjunct in fondaparinux-treated patients has been agreed as part of the Risk Management Plan *(for a more detailed discussion, see page 19-21 of this report)*. Sections 4.2 and 4.4 of the SPC include guidance on the use of UFH during PCI in both UA/NSTEMI and STEMI patients (non-primary PCI), and section 4.4 contains a warning on the risk of guiding catheter thrombus in PCI.

The non-bleeding adverse event profile reported in the ACS program is consistent with the adverse drug reactions identified for VTE prophylaxis and does not give rise to concern. As reflected in section 4.8 of the SPC, the most commonly reported adverse events in OASIS-5 were headache, chest pain and atrial fibrillation, whereas atrial fibrillation, pyrexia, chest pain, headache, ventricular tachycardia, vomiting, and hypotension were most commonly reported in OASIS-6.

Finally, there is extensive experience in patients with moderate renal impairment and limited experience in patients with severe renal impairment (CrCl 20-30 ml/min) with treatment for up to 8 days in the ACS programme, as reflected in section 4.4 of the SPC. Treatment duration was similar in the different renal function groups, and there was no evidence of more bleedings at later time points in patients with reduced renal function (i.e. when these patients obtain higher exposure). In OASIS 5 the incidence of bleedings is lower in patients with moderate to severe renal impairment receiving fondaparinux than in patients receiving enoxaparin. In OASIS 6, the incidence of bleeding in patients with CrCl >20 ml/min receiving fondaparinux is low. Sections 4.2 and 4.4 of the SPC clearly state that the maximum treatment duration in these indications is 8 days. Thus, in contrast to the approved dosing recommendations for prophylaxis of VTE, no dose reduction is proposed in patients with ACS and with impaired renal function; fondaparinux is contraindicated in patients with CrCl <20 ml/min).

Conclusions and Benefit/Risk Assessment

OASIS-5 and OASIS-6 are two large, well designed and conducted studies adequately covering the spectrum of Acute Coronary Syndromes.

The results of OASIS-6 demonstrated a clinically relevant and statistically significant risk reduction of fondaparinux relative to control death or re-MI in the overall STEMI population. Consistent with this result, treatment with fondaparinux was superior to placebo but failed to demonstrate superiority over UFH. Treatment with fondaparinux also significantly reduced all cause mortality at Day 30 in the overall population and in stratum 1 (vs. placebo). Fondaparinux showed a comparable safety profile to the respective controls. However, in patients undergoing PCI, fondaparinux did not provide any benefit compared to control, with a clear trend observed in favour of the control group. Coupled to the higher incidence of severe haemorrhage and serious coronary complications in this subgroup, the benefit:risk balance in STEMI patients undergoing PCI is negative and these patients have been excluded from the indication proposed by the Applicant. For the remainder of the STEMI population, namely *patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy*, the benefit:risk balance is positive.

Regarding the UA/NSTEMI population, OASIS-5 showed that treatment with fondaparinux was non-inferior to enoxaparin in the early prevention of adjudicated death, MI or RI at Day 9. In addition, fondaparinux was associated with a significant reduction in all-cause mortality at Day 30. Importantly, treatment with fondaparinux resulted in a significant lower risk of major bleeding up to and including

day 9 compared to treatment with enoxaparin. However, in the PCI subgroup there was no significant advantage of fondaparinux over enoxaparin, and there were clear safety concerns regarding the higher incidence of coronary complications observed during the PCI procedure. Hence, in order to maintain a positive benefit:risk balance in the UA/STEMI population, the indication has been restricted to *patients for whom urgent (<120mins) invasive management (PCI) is not indicated*, and fondaparinux should not be used as the sole anticoagulant in patients undergoing non-primary PCI. These patients should be managed with UFH as per local practice. A Post-Authorisation Safety Study to further evaluate the safety of this proposed PCI management strategy has been agreed as part of the RMP.