London, 15 November 2007
Product Name: **Angiox**
EMEA/H/C/562/II/08

SCIENTIFIC DISCUSSION

1. Introduction

On 7 December 2006 the applicant submitted a type II variation to extend the indication to include *treatment of patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)*. The change is requested on the basis of data from a large phase III study (ACUITY/TMC-BIV-08-02) evaluating the use of bivalirudin as a treatment for patients with ACS (UA/NSTEMI). There are consequential changes to sections 4.1, 4.2, 4.8 and 5.1 of the SPC as a result of this application. In addition, the Applicant has taken the opportunity to update the product information according to the latest QRD template.

2. Clinical aspects

Applicant's Rationale for the new indication

Heart disease causes more deaths and disability and incurs greater economic costs than any other illness in the western world. Despite improved efforts in the prevention of heart disease, 2.5-3.0 million persons are admitted to European and US hospitals every year with ACS.

An early invasive strategy consisting of angiography followed by either percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or medical management, results in enhanced survival compared to conservative care, and is recommended by the European Society of Cardiology (ESC) Guidelines [Betrand et al, 2002] and the American Heart Association/American College of Cardiology (AHA/ACC). In the era of potent antiplatelet therapy and coronary stents, early invasive therapy of NSTE-ACS patients decreases mortality by 25% at a mean of 2 years of follow-up, compared with a more conservative approach.

Aspirin (ASA), clopidogrel, a glycoprotein IIb/IIIa inhibitor (GPI), and an antithrombin agent [either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)] are all recommended in the management of patients with ACS. Even with this intensive adjunct pharmacologic regimen rates of death and myocardial infarction (MI) are not negligible and haemorrhagic complications are frequent.

The combination of potent adjunct therapy and invasive management inevitably increases the risk of bleeding. Historically bleeding has been regarded as a safety variable. More recently there is growing awareness of bleeding as a predictor of morbidity and mortality.

Major bleeding is associated with increased incidence of other cardiac events (MI, repeat angioplasty), longer hospital stay, and higher resource utilisation. In large registries and meta-analyses of clinical trial databases, bleeding has been established as a predictor of mortality in ACS and a step-wise increase in mortality is associated with increasing bleeding severity. In-hospital major bleeding has a 4-fold higher risk of 1-year mortality. Even the need for transfusion, examined in isolation, is an independent predictor of 1-year mortality.

An effective treatment of ACS should prevent further chest pain and MI with minimal bleeding consequence and allow the patient to progress to management through angiography and definitive treatment via revascularisation with PCI or CABG or continued medical management.

A primary endpoint that encompasses both the ischaemic and bleeding periprocedural complications would be considered an appropriate reflection of the global morbidity and mortality burden associated with the respective adjunctive antithrombotic regimens.

Clinical Data

The efficacy of bivalirudin for the proposed additional indication is supported by data from a single pivotal study (ACUITY - *Acute Catheterisation Urgent Intervention Triage Strategy*) and two supportive studies (TIMI 7 & TIMI 8 -*Thrombolysis In Myocardial Infarction*-). A brief overview of these trials is shown in the table 1 below.

Table 1: Comparison of study design features across the pivotal and supportive ACS trials

Design features	ACUITY trial	TIMI 7 trial	TIMI 8 trial
Total enrolled	13,819	420	133
Blinding	Open	Double-blind	Double-blind
Randomisation	Randomised	Randomised	Randomised
Bivalirudin dose	0.1 mg/kg bolus + 0.25 mg/kg/h infusion through angiography or as long as needed; for patients undergoing PCI an additional 0.5 mg/kg bolus + 1.75 mg/kg/h infusion for duration of PCI	Doses from 0.02 mg/kg/h infusion to 1.0 mg/kg/h infusion for 72 hours	0.1 mg/kg/bolus + 0.25 mg/kg/h infusion for up to 72 hours
GPI use with bivalirudin	Planned in Arm B, Provisional in arm C (6.5%)	NA	NA
Comparator	Heparin (UFH or enoxaparin) + Planned GPI	None	Heparin
Comparator dose	60 U/kg bolus and 12 U/kg/h infusion to target an ACT of 200 to 250 seconds for PCI Enoxaparin 1.0 mg/kg every 12 hours until angiography	None	70 U/kg bolus + 15 U/kg/h for 12 to 72 hours
Concomitant medication	Aspirin (required) Clopidogrel (recommended)	Aspirin	Aspirin
Primary evaluation period	Day 30 follow-up visit (30±5 days post-randomisation)	72 hours from initiation of infusion	(First of) Discharge or within 14 days of randomisation
Centres (Countries)	450 (17)	29 (2)	13 (1)
Adjudicated Endpoints	Blinded adjudication of Death, MI, Unplanned revascularisation for ischaemia, Bleeding, Subacute thrombosis	Death, MI, non-ischaemic clinical deterioration requiring angiography	MI and Major haemorrhage
Clinical Endpoints	Death, MI, Unplanned revascularisation for ischaemia, Major bleeding	Death, MI, Recurrent ischaemia, Non-ischaemic clinical deterioration requiring angiography, Major haemorrhage	Death, MI, haemorrhage

ACUITY (Acute Catheterisation Urgent Intervention Triage Strategy) Trial

This study compared bivalirudin with heparin (UFH or enoxaparin) in patients undergoing early invasive management for ACS without ST-segment elevation. The study was conducted at 450 centres in North America, Europe, Australia and New Zealand.

Initially, the MAH submitted 30-day data. This was subsequently complemented with 1-year data.

The main *objective* (Primary Randomisation) of this trial was to determine the optimal antithrombotic treatment regimen for patients with moderate or high-risk ACS managed by early angiography followed by medical management, PCI, or CABG. The second main objective (Secondary Randomisation) was to evaluate the clinical impact of the timing of GPI administration, either upfront or deferred until PCI is performed.

Design

This was an open-label, multicentre, prospective, randomised and parallel group study. It examined the role of bivalirudin in treating patients with moderate or high-risk ACS (UA and NSTEMI) undergoing an early invasive strategy, and evaluating the clinical impact of a treatment strategy based

on the timing of GPI initiation. Patients were treated with ASA (required) and a thienopyridine (preferred), and were randomised into one of 3 treatment arms as follows:

- Arm A: heparin (UFH or enoxaparin) with GPI administration
- Arm B: bivalirudin with GPI administration
- Arm C: bivalirudin alone

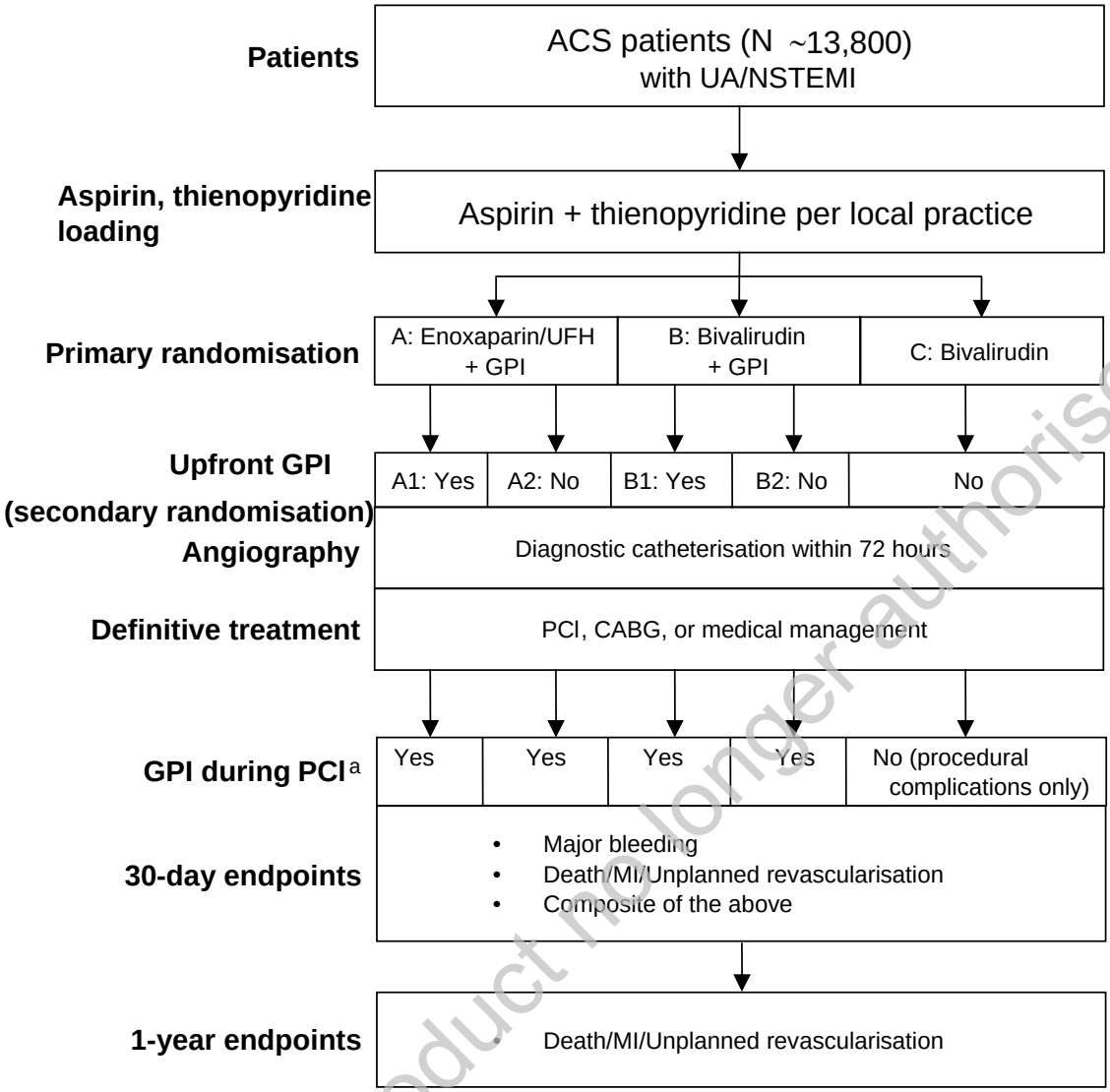
The study design is depicted in Figure 1.

In the original study protocol, the sole comparator treatment in Arm A was enoxaparin. The choice of UFH or enoxaparin was introduced by a protocol amendment in light of results from two clinical studies that concluded that major bleeding was higher on enoxaparin than UFH. After the protocol amendment each site had to make a choice between enoxaparin and UFH that would be applied to all patients subsequently included in the study at that site. Based on their centre practice, each ACUITY investigator was required to declare in advance whether all patients randomised to Arm A at their site would receive enoxaparin or UFH. Therefore, the choice of enoxaparin or UFH was predetermined for all patients at a given site, and was not varied on a patient-by-patient basis. The exception to this rule was for individual patients who had been receiving UFH or a LMWH before randomisation; these patients were to be maintained on the same type of heparin after randomisation to avoid any switching from one antithrombotic agent to the other.

Randomisation was to be stratified centrally according to the use of thienopyridine before angiography or after angiographic triage. In a second stage of randomisation, using a 2×2 factorial design, patients assigned to GPI administration (Arms A and B) were randomised to begin GPI administration either upfront (prior to angiography) or at the time of PCI (GPI during PCI). This secondary randomisation is referred to as the ACUITY Timing Trial.

Angiography was to be performed within 72 hours of randomisation, followed by triage to medical, PCI, CABG. Patients were followed up until hospital discharge or Day 7, 30, and at 1 year after randomisation.

Figure 1: ACUITY study design



[a] Patients receiving upfront GPI continued to receive GPI during PCI.

Number of patients (planned and analysed)

A total of 13,800 patients were to be included in the study into 3 randomised groups. The number actually included was 13,819 (Arm A – 4603, Arm B – 4604 and Arm C – 4612).

Three datasets were used in analyses: ITT (Patient randomised treatment assignment), PP (All randomised patients who received at least one dose of the study drug) and ATP – as treated patients (all patients who received at least one dose of randomised study drug post-randomisation, irrespective of randomised treatment assignment). In the ATP analysis, if the patient received more than one study drug during the study, the first study drug after randomisation was used in the analysis.

The number of patients included in the ITT population were 4603 in arm A, 4604 in arm B, and 4612 in arm C. The numbers for PP population were 4553, 4520 and 4555 respectively. Following secondary randomisation, the following number of patients were included in Arms A and B of the ITT populations: 2294 (heparin with upfront GPI, Arm A1), 2309 (heparin with GPI during PCI arm, Arm A2), 2311 (bivalirudin with upfront GPI, Arm B1), and 2293 (bivalirudin with GPI during PCI, Arm B2).

Inclusion criteria

Patients were required to present with chest pain symptoms that included at least 10 minutes of angina or anginal equivalent that the investigator believed had a high likelihood of being ischaemic in origin,

consistent with a diagnosis of UA/NSTEMI, and to meet at least one of the following four UA/NSTEMI criteria:

i) All of the following four features: Age ≥65 years, ASA taken within the previous 7 days, two or more episodes of angina in the previous 24 hours and three or more of the following risk factors: hypertension, high cholesterol, family history, diabetes, current smoker, ii) ECG changes: new or presumably new ST-segment depression ≥0.1 mV (≥1 mm), or transient (<30 minutes) ST-segment elevation ≥0.1 mV (≥1 mm) in at least two contiguous leads, iii) Abnormal cardiac biomarker within 24 hours before enrolment, defined as elevated troponin I, T, or CPK-MB greater than the site's ULN, iv) History of CAD with documentation of one of the following: Prior angiography (coronary stenosis of >50%), Prior PCI or CABG and prior definite, documented MI.

Dose and mode of administration

Bivalirudin was administered intravenously (IV) to patients in treatment arms B and C as follows: after randomisation and prior to angiography, all patients were to receive an initial bolus dose of 0.10 mg/kg of bivalirudin, followed by a 0.25 mg/kg/h infusion continued through angiography. Subsequent dosing depended on whether the patient was triaged to medical management, PCI, or CABG (on- or off-pump). Patients triaged to medical management or CABG were to be continued on this dose per physician discretion or up to 1 hour prior to CABG. For patients triaged to PCI, an additional bivalirudin bolus dose of 0.5 mg/kg was given followed by a 1.75 mg/kg/h infusion for the duration of the procedure. After PCI, a 0.25 mg/kg/h infusion could be administered for 4 to 12 hours in the absence of a GPI.

Heparin (UFH or enoxaparin), was administered as follows:
UFH: Prior to angiography, an initial bolus dose of 60 U/kg IV randomisation, followed by a 12 U/kg/h infusion continued through angiography.

Enoxaparin: Prior to angiography, a subcutaneous (SC) dose of 1.0 mg/kg every 12 hours until angiography. For patients triaged to medical management, PCI, staged PCI, or CABG (on- or off-pump), subsequent dosing was based on the guidelines provided in the study protocol. In particular, iv 0.3 or 0.75 mg enoxaparin was administered in patients undergoing PCI, depending on the timing between the PCI procedure and the last sc enoxaparin dose. This pre-PCI iv enoxaparin administration is not approved in the EU. However, according to the MAH, there is also a recognised need in the EU for additional anti-thrombotic therapy for patients receiving enoxaparin ahead of their intervention. The latest ESC guidance for ACS recommend an additional 0.3 mg/kg IV dose of enoxaparin for patients who received their last dose > 6 - 8 hours before their PCI. Moreover, emerging clinical practice was a consideration in the design of the ACUITY trial and the supplemental IV bolus of enoxaparin in ACUITY was, in part, driven by the dosing recommendations used in the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial.

Duration of treatment

Patients received at least one dose of randomised study treatment prior to undergoing angiography, and administration continued during angiography. Subsequent dosing duration depended on whether the patient was triaged to medical management, PCI, or CABG (on- or off-pump).

Endpoints

The *primary* endpoints were the following, measured at Day 30:

1. Composite ischaemic endpoint: incidence of all-cause death, MI, or unplanned revascularisation for ischaemia.
2. Composite "net clinical outcome": incidence of all-cause death, MI, unplanned revascularisation for ischaemia, or major bleeding (ACUITY scale – see later under safety section).
3. Major bleeding (ACUITY scale).

The *secondary* endpoints were:

1. The composite primary endpoints "in-hospital" and components of the composite endpoints (including the composite rate of death and nonfatal MI) "in-hospital" and at the Day 30 visit.
2. Incidence of new-onset thrombocytopenia.
3. Incidence of adverse events other than components of the primary endpoints.
4. Rehospitalisation.
5. Duration of index hospitalisation (hospital where angiography was performed)

Statistical considerations

To minimise any bias introduced by the open label design all clinical components of the primary and secondary endpoints (deaths, MIs, unplanned revascularisations for ischaemia, major bleeding events, cases of coronary thrombosis and cardiac biomarker MIs) were clearly and objectively pre-defined and independently and centrally adjudicated using original source documentation for each patient by a Clinical Events Committee (CEC) blinded to the assignment of study treatments. Also, the adjudicated data were not shared with the study sites, and were maintained at the CEC. According to the Applicant the bias introduced due to the open label design is likely to be small especially as the study was very large and was conducted at around 600 sites in different parts of the world. Also each patient was maintained on the same heparin throughout the treatment period. Switching between UFH and enoxaparin was not permitted unless the patient was triaged to CABG (in which perioperative UFH was to be used), or unless there was a definite clinical indication for using a different anticoagulant.

Further to a request from CHMP pertaining to the possibility of study bias, in particular for the revascularisation endpoint, where the knowledge of which treatment a patient was receiving could have influenced the revascularisation endpoint, the Applicant clarified the precautions taken regarding the 'unplanned revascularisation for ischaemia'. This endpoint consisted of one of the following four individual objective components: i) Symptoms or signs of cardiac ischaemia, or ii) A positive functional study ("stress test"), or iii) A target lesion with diameter stenosis >70% by quantitative coronary angiography, or iv) Operator assessment of >80% in the absence of core laboratory analyses. The CEC reviewed original source documentation from all patients with a suspected revascularisation event for final verification that a revascularisation did occur *and* it was driven by ischaemia.

The primary analyses of efficacy were performed for the ITT population. Analyses for the PP population served as confirmatory and sensitivity analyses. These analyses included the statistical tests (of three levels) in sequential order given in table 11 below. The Hochberg multiple comparison method was used at each level.

Table 11: Primary analyses of 30-day endpoints

Level	Arm B versus Arm A	Arm C versus Arm A
1	Noninferiority (/superiority) of composite net clinical outcome endpoint	Superiority of bleeding endpoint
2	Noninferiority (/superiority) of composite ischemic endpoint	Noninferiority (/superiority) of composite net clinical outcome endpoint
3	Noninferiority (/superiority) of bleeding endpoint	Noninferiority (/superiority) of composite ischemic endpoint

The analyses started at level 1; if both tests of Arm B vs Arm A and Arm C vs Arm A were significant at the 1-sided significance level α=0.025, the comparisons between Arm B vs Arm A and Arm C vs Arm A were performed at level two at α=0.025 and the Hochberg procedure again applied. If one of the level 1 tests failed at α=0.025, further tests for the corresponding comparisons at levels 2 and 3 were not to be performed. If the test for the other level 1 comparison was significant at the 1-sided significance level of α=0.0125, then the subsequent tests for this comparison at levels 2 and 3 would also be performed at the level of α=0.0125. To proceed from level 2 to level 3, the same criteria for significance were applied. The tests at subsequent levels were to be performed regardless of the results of the superiority tests. To establish a single non-inferiority test of bivalirudin (Arm B or Arm C) against heparin (Arm A) on risk difference at a 1-sided significance level of α, the 100(1– α) % 1-

sided CI for the difference of the event rate (bivalirudin – heparin) was obtained. If the upper limit of the CI was less than a pre-specified margin (25% of the observed event rate in Arm A), the non-inferiority of the bivalirudin treatment was to be declared. The superiority test was to be performed only if non-inferiority was established. If the upper limit of the same CI for the difference of the event rate (bivalirudin – heparin) was < 0, the superiority of the bivalirudin treatment was to be declared.

Results

Baseline Data

A total of 13,819 subjects were randomised to treatment. All 3 groups were balanced in terms of diagnostic criteria. The median age was around 63 years, around 30 % were female and 88% were white. High risk patient characteristics of the ACUITY population that mandated angiography within 72 hours were balanced across the three treatment arms. The approximate figures are: 77% of patients had recurrent ischaemia, 70% had dynamic ECG changes or elevated cardiac biomarkers, 28% had diabetes and 99% of patients underwent angiography within 72 hours.

The figures for the patient triage following angiographic assessment are as follow: medical management (33%), PCI (56%) and CABG (11%).

EFFICACY RESULTS

The results of the primary endpoints are summarised in tables 40 and 41 below.

Table 40: Clinical endpoints at the Day 30 visit: Arm C (bivalirudin alone) verses Arm A (heparins + GPI) – ITT population

Endpoint	Heparins + GPI (A) N=4603, n (%)		Bivalirudin alone (C) N=4612, n (%)		Diff. C- A	95% CI
ACUITY-scale major bleeding [a]	262	(5.7)	139	(3.0)	-0.0268	(-0.0351,-0.0184)*
Net clinical outcome endpoint [b]	538	(11.7)	466	(10.1)	-0.0158	(-0.0286, -0.0031) + *
Composite ischemic endpoint [c]	334	(7.3)	360	(7.8)	0.0055	(-0.0053, 0.0163) +

[a] Protocol non-CABG major bleeding (defined in Section *9.5.2.5.1, p.77*).
[b] Composite endpoint of death, MI, unplanned revascularization, and major bleeding.
[c] Composite endpoint of death, MI, unplanned revascularization.
+ indicates that noninferiority of bivalirudin alone to heparins + GPI has been shown based on the noninferiority margin of 25 % of the observed events rates in Arm A
* indicates that superiority of bivalirudin alone to heparins +GPI has been shown.

Bivalirudin alone (group C) was superior to the standard treatment (group A) in terms of ACUITY-scale major bleeding and the net clinical outcome endpoint. According to the preset 25% non-inferiority constraint, it was also non-inferior to the standard treatment arm for the composite ischaemic endpoint, as the upper limit of the 95% CI for the difference in percentages for the composite endpoint (1.63%) was less than 1.825%.

Table 41: Clinical endpoints at the Day 30 visit: Arm B (bivalirudin + GPI) verses Arm A (heparins + GPI) – ITT population

Endpoint	Heparins + GPI (A) N=4603, n (%)		Bivalirudin + GPI (B) N=4604, n (%)		Diff. B - A	95% CI
Net clinical outcome endpoint [a]	538	(11.7)	541	(11.8)	0.0006	(-0.0125, 0.0138) +
Composite ischemic endpoint [b]	334	(7.3)	356	(7.7)	0.0048	(-0.0060, 0.0155) +
ACUITY-scale major bleeding [c]	262	(5.7)	243	(5.3)	-0.0041	(-0.0134, 0.0052) +

[a] Composite endpoint of death, MI, unplanned revascularization, and major bleeding.
[b] Composite endpoint of death, MI, unplanned revascularization.
[c] Protocol non-CABG major bleeding (defined in Section *9.5.2.5.1, p.77*).
+ indicates that noninferiority of bivalirudin + GPI to heparins + GPI has been shown based on the noninferiority margin of 25 % of the observed events rates in Arm A

The bivalirudin + GPI arm (group B) was non-inferior to the standard treatment arm (group A) for the net clinical outcome endpoint, the composite ischaemic endpoint and the major bleeding endpoint. To achieve non-inferiority for these three endpoints the upper limit of the 95% confidence intervals had to be less than 2.925%, 1.825%, 1.425%, respectively. The results for the PP population are very similar to the ITT population.

Regarding secondary endpoints, the individual components of the composite ischaemic endpoint at Day 30 are summarised in the tables 44 and 45 below.

Table 44: Components of the composite ischemic endpoint at the Day 30 visit: Arm C (bivalirudin alone) verses Arm A (heparins + GPI) – ITT population

Endpoint component	Heparins + GPI (A) N=4603, n (%)		Bivalirudin alone (C) N=4612, n (%)		Diff. C - A	95% CI
Death or MI	272	(5.9)	302	(6.5)	0.0064	(-0.0035, 0.0163)
Death	62	(1.3)	74	(1.6)	0.0026	(-0.0023, 0.0075)
MI	227	(4.9)	248	(5.4)	0.0045	(-0.0046, 0.0135)
Unplanned revascularization	105	(2.3)	110	(2.4)	0.0010	(-0.0051, 0.0072)

Table 45: Components of the composite ischemic endpoint at the Day 30 visit: Arm B (bivalirudin + GPI) verses Arm A (heparins + GPI) – ITT population

Endpoint component	Heparins + GPI (A) N=4603, n (%)		Bivalirudin alone (B) N=4604, n (%)		Diff. B - A	95% CI
Death or MI	272	(5.9)	286	(6.2)	0.0030	(-0.0067, 0.0128)
Death	62	(1.3)	70	(1.5)	0.0017	(-0.0031, 0.0066)
MI	227	(4.9)	229	(5.0)	0.0004	(-0.0084, 0.0093)
Unplanned revascularization	105	(2.3)	123	(2.7)	0.0039	(-0.0024, 0.0103)

There was a numerical increase in Death, MI and Unplanned revascularisation in both of the bivalirudin arms with respect to the control arm (A). The number of deaths was even higher in bivalirudin alone arm (arm C), which is of clinical concern.

Results of the composite ischaemic endpoint and its components at 1-year

In the light of the concerns raised with the results of the composite ischaemic endpoint at Day 30, the CHMP requested an efficacy analysis of 1-year ischaemic data. The absolute differences between the treatment groups for the composite ischaemic endpoint and for the individual components thereof data shown in tables 2 and 3 below.

Table 2: Composite ischaemic endpoint and its components at the 1 year follow-up visit; Arm C vs. Arm A

Endpoint	Heparin + GPI (A) N=4603, n (%)	Bivalirudin alone (C) N=4612, n (%)	Diff.* C – A	95% CI
Composite ischaemic endpoint	702 (15.3)	736 (16.0)	0.0071	(–0.0077, 0.0219)
Death	178 (3.9)	170 (3.7)	-0.0018	(–0.0096, 0.0060)
MI	312 (6.8)	351 (7.6)	0.0083	(–0.0022, 0.0189)
Unplanned revascularisation	371 (8.1)	389 (8.4)	0.0037	(–0.0075, 0.015)

* Risk difference between Arm C – Arm A.

Table 3: Composite ischaemic endpoint and its components at the 1 year follow-up visit; Arm B vs. Arm A

Endpoint	Heparin + GPI (A) N=4603, n (%)	Bivalirudin + GPI (B) N=4604, n (%)	Diff.* B– A	95% CI
Composite ischaemic endpoint	702 (15.3)	732 (15.9)	0.0065	(–0.0083, 0.0213)
Death	178 (3.9)	176 (3.8)	-0.0004	(–0.0083, 0.0074)
MI	312 (6.8)	321 (7.0)	0.0019	(–0.0084, 0.0123)
Unplanned revascularisation	371 (8.1)	407 (8.8)	0.0078	(–0.0036, 0.0192)

* Risk difference between Arm B – Arm A.

Statistically, the results were very similar in all three treatment groups. For both the bivalirudin alone arm and the bivalirdin + GPI groups the upper limit of the 95% CI for the difference from the reference arm (heparin + GPI) was about 2%. For death the upper limit of the CIs were 0.6% for the comparison between group C and group A and 0.74% for the comparison between group B and group A. For the MI endpoint the figures were 1.89% and 1.23% respectively and for unplanned revascularisation 1.5% and 1.92%. All of these comparisons give very narrow confidence intervals and provide good evidence that treatment groups B and C are comparable on the three components of the composite ischaemic endpoint.

Clinically, the worrying trend observed for the triple ischaemic endpoint at D-30 is not reproduced at 1 year. There is no evidence of increased mortality in the bivaluridin group (arms B and C). Statistically this is true for other components too.

The Kaplan Meier plots below show that the numerical differences in death and in the composite ischaemic endpoint observed at Day 30 were not associated with differences in long term outcomes as evaluated at 1 year (Figures 2 and 3 below).

Fig 2: Time to death at the 1-year follow-up visit based on Kaplan Meier method: Arm B (bivalirudin + GPI) and Arm C (bivalirudin) versus Arm A (heparin + GPI) - ITT population

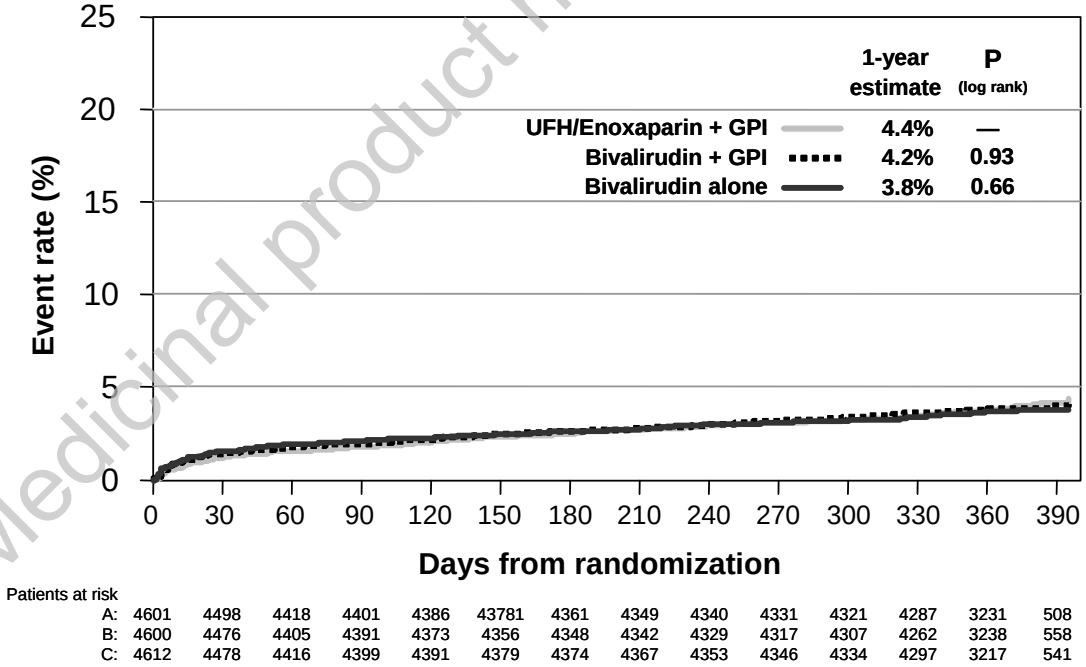
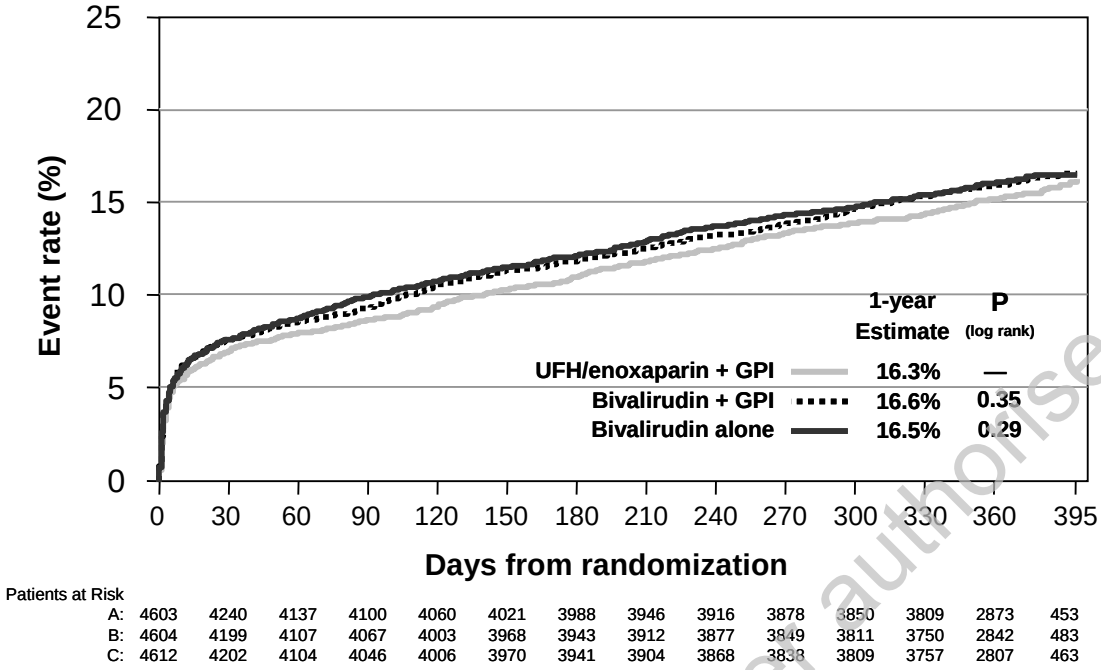


Fig 3: Time to first occurrence of the composite ischaemic endpoint at the 1-year follow-up visit based on Kaplan-Meier method: (bivalirudin + GPI) and bivalirudin vs heparin + GPI – ITT population



Patients at Risk

A:	4603	4240	4137	4100	4060	4021	3988	3946	3916	3878	3850	3809	2873	453
B:	4604	4199	4107	4067	4003	3968	3943	3912	3877	3849	3811	3750	2842	483
C:	4612	4202	4104	4046	4006	3970	3941	3904	3868	3838	3809	3757	2807	463

Time to first occurrence = time to first component event (death, MI, unplanned revascularisation for ischaemia) of the composite ischaemic endpoint.

Table 4 below shows the composite ischaemic results at 1 year according to the actual procedure undergone by the patient following angiographic assessment.

Table 4: Composite ischaemic endpoint according to actual procedure at 1-year follow-up visit

Endpoint	Heparin + GPI (A) N=4603, n (%)	Bivalirudin + GPI (B) N=4604, n (%)	Bivalirudin alone (C) N=4612, n (%)
Composite ischaemic endpoint (overall)	702 (15.3)	732 (15.9)	736 (16.0)
PCI (n=5180)	456/2531 (17.8)	507/2609 (19.4)	502/2619 (19.2)
Medical management (n=2995)	134/1493 (9.0)	134/1496 (9.0)	131/1502 (8.7)
CABG (n=1040)	112/549 (20.4)	91/499 (18.2)	103/491 (21.0)

There are no significant differences observed between the groups. As expected, there were lower event rates observed in patients who were medically managed versus those who underwent PCI or CABG, due in part to less significant extent of disease as well as the lack of invasive therapy.

Further to a request from CHMP, the Applicant provided an analysis of all MIs at 30 days and at 1 year indicating the categories of MI according to established definitions (i.e. enzyme/troponin defined, ECG confirmed, both or any criteria).

There was no difference in the 3 treatment groups for Q-wave MI, both at 30 day and at 1-year. In-hospital enzyme data showed no difference in groups A, B and C for CKMB elevations of >8ULN and for CKMB <3ULN. There was a modest increase in those with CKMB between 3-8ULN, which has to be balanced against a clear bleeding advantage.

Results of ACUITY Timing Trial (secondary randomisation)

The purpose of the ACUITY Timing Trial was to evaluate the clinical impact of the timing of GPI administration, either upfront (prior to angiography) or deferred until PCI, and the results are shown in table 5 below.

Table 5: ACUITY timing trial day 30 and 1 year results, including Arm C

Endpoint	Upfront GPI (A1+B1) N=4605, n (%)	Deferred GPI (A2+B2) N=4602, n (%)	Bivalirudin alone (C) N=4612, n (%)
30-day outcomes			
Composite ischaemia	328 (7.1)	369 (8.0)	361 (7.8)
Major bleeding	281 (6.1)	224 (4.9)	140 (3.0)
Net clinical outcome	543 (11.8)	542 (11.8)	468 (10.1)
1-year outcomes			
Composite ischaemia	693 (15.0)	741 (16.1)	736 (16.0)
Death	173 (3.8)	181 (3.9)	170 (3.7)

There were no significant differences in efficacy outcomes based on the timing of GPI administration at Day 30 or at 1-year. There was a reduction in bleeding for bivalirudin monotherapy compared to either GPI timing strategy. There was no significant interaction (on formal interaction testing) between upstream or deferred GPI administration and bivalirudin monotherapy.

Subgroup analyses and Post-hoc analyses

Subgroup analyses investigating the potential influence of several predefined factors on the main clinical endpoints compared bivalirudin alone (Arm C) versus heparins + GPI (Arm A) and bivalirudin

+ GPI (Arm B) versus heparins + GPI (Arm A) using risk ratios. There were no statistically significant differences among the treatment arms for incidences of death, MI (including Q-wave MIs, non-Q-wave MIs, or large MIs), or unplanned revascularisation at the Day 30. Results of treatment comparisons on the three main clinical endpoint variables were consistent regardless of whether the patient was triaged to medical management, PCI, or CABG. There were no differences in efficacy outcomes when GPI was administered upfront or at the time of PCI.

The results of the composite ischaemic endpoint at 1 year show a numerical increase in ischaemic events in the bivalirudin alone arm in EU patients, in diabetics, in patients with creatinine clearance <60, in patients who did not receive thienopyridine or who received it post-angiography or PCI patients, in CABG, in patients who were randomised to angiography between 3.0-19.7 hours and those randomised late (≥19.7 hrs). A similar pattern of increased ischaemic events for patients who received bivalirudin + GPI was observed in women, patients of other race, EU patients, diabetes mellitus, CrCl <60, patients who did not receive thienopyridine, early and intermediate randomisation of angiography and use of GPI during PCI.

As regards the results of death at 1 year, there was an adverse numerical increase in patients <65, patients of other race, diabetics, patients with CrCl <60, those not receiving thienopyridine, CABG patients and patients randomised to angiography treated with bivalirudin alone. Similar trends were noted for patients receiving bivalirudin + GPI.

Further to a request from CHMP to better characterise a target group where the benefit/risk of bivalirudin treatment (monotherapy or combined with GPI) is clearly positive, the Applicant submitted 30-day and 1-year results for patients who received ASA and clopidogrel. Clopidogrel was strongly encouraged in ACUITY and dosing and timing was left to the discretion of local institutional practice. The protocol recommended 300 mg loading dose prior to angiogram or PCI, but at no time later than 2 hours after PCI, if PCI was performed. The majority of patients (88.3%) received clopidogrel during index hospitalization and 63.3% received clopidogrel prior to angiogram or PCI. The results of the composite ischaemic endpoint at 30 days and 1 year in patients who received clopidogrel prior to angiogram or PCI are shown in table 6.

Table 6: ACUITY trial; 30-day and 1-year risk ratios for the composite ischaemic endpoint and its components for patients that received ASA and clopidogrel as per protocol.*

	Patients receiving aspirin & clopidogrel as per protocol				
	Arm A Heparin + GPI (N=2842) %	**Arm B bival +GPI (N=2924) %**	**B/A Risk ratio (CI)**	**Arm C bival alone (N=2911) %**	**C/A Risk ratio (CI)**
30 day					
Composite ischaemia	7.4	7.4	1.00 (0.84, 1.21)	7.0	0.95 (0.79, 1.15)
Death	1.4	1.4	1.00 (0.64, 1.54)	1.2	0.90 (0.57, 1.41)
MI	4.8	4.9	1.01 (0.80, 1.27)	4.7	0.98 (0.78, 1.24)
Unplanned revasc.	2.6	2.8	1.09 (0.80, 1.49)	2.2	0.84 (0.61, 1.18)
1-year					
Composite ischaemia	16.1	16.8	1.04 (0.93, 1.17)	15.8	0.98 (0.87, 1.10)
Death	3.7	3.9	1.06 (0.81, 1.37)	3.3	0.90 (0.69, 1.18)
MI	6.7	7.3	1.09 (0.90, 1.32)	6.8	1.03 (0.85, 1.25)
Unplanned revasc.	9.4	10.0	1.06 (0.91, 1.24)	8.9	0.94 (0.80, 1.11)

*clopidogrel pre-angiography or pre-PCI

The above results clearly show that the incidence of composite ischaemia, death, MI and unplanned revascularisation was similar in all three groups (A, B & C) while showing reduction in bleeding in group C (see results under safety), demonstrating a favourable a risk:benefit in patients treated with bivalirudin alone or in combination who have received ASA and clopidogrel.

Further to a request from CHMP, the MAH presented a *post-hoc* analysis on patients who received supplemental IV doses of enoxaparin. In terms of the patients affected, a total of 1262 patients received enoxaparin as randomized treatment pre-PCI in ACUITY. Of these, 20% (258 patients) received a median 0.3 mg/kg additional IV bolus of enoxaparin.

Table 7: 30 day outcome comparison of supplemental vs no supplemental IV enoxaparin dose

	Patients randomized to Arm A and receiving enoxaparin		
Category	Supplemental enox dose (median 0.3 mg/kg IV) N=258	No supplemental enox IV dose N=1004	p-value[a]
30 day outcomes			
Composite ischaemia	21 (8.1%)	98 (9.8%)	0.43
Death	1 (0.4%)	15 (1.5%)	0.16
ACUITY-scale non-CABG major bleeding	17 (6.6%)	60 (6.0%)	0.71
1-year outcomes			
Composite ischaemia	43 (16.7%)	186 (18.5%)	0.49
Death	10 (3.9%)	37 (3.7%)	0.88

[a] Chi-Square test.

Although these data must be interpreted with caution, there would appear to be no difference in clinical outcomes, including bleeding, between patients who received the additional IV dose of enoxaparin and those who underwent PCI and did not. This provides reassurance that the results of the control group were not influenced by this recommended dosing practice.

Points raised on trial design

One of the initial points raised by CHMP was the open-label nature of the trial. The MAH argues that the complexities involved in the clinical management of patients with ACS did not allow a double-blind approach to masking the identities of study treatments or the timing of GPI initiation. Therefore, a number of strategies were used to minimise bias.

Death is the ultimate measure of objective clinical outcomes. Every site-reported death in ACUITY was independently adjudicated; there was 100% concordance for death based on CEC data. To avoid potential bias in the reporting of MI, definitions of MI were carefully and prospectively defined. Measurements used to quantify MI were standardised and all MI events were independently adjudicated by a blinded CEC. Thus, for the hard clinical endpoints (death and MI) it is considered unlikely that the results are biased to such an extent to affect the conclusions drawn due to the study being open label. It remains possible that bias could have been introduced that affected the results for the revascularisation endpoint. The blinded CEC reviewed original source documentation from all patients with a suspected revascularisation event for final verification that a revascularisation did occur *and* it was driven by ischaemia. It is also important to note that the revascularisation event rate was small compared to the more objective endpoint event rates of MI and death and therefore the contribution of any potential bias arising from an assessment of unplanned revascularisation would be relatively minor.

3.2.2. Safety

The safety information for the proposed indication of ACS includes data from more than 14,000 patients enrolled in ACUITY, TIMI 7 and TIMI 8 (C93-309-P). Both TIMI 7 & TIMI 8 trials were conducted in patients with ACS (UA/NSTEMI) before an early invasive strategy was considered the recommended treatment. The TIMI 8 study was terminated early for commercial reasons after 133 of the planned 5,320 patients had been randomised.

In total clinical trial experience with bivalirudin is based on approximately 25,100 patients studied in healthy volunteers, renally-impaired patients and in patients with various underlying cardiovascular/haematological conditions. The number of control patients was approximately 20,000.

Safety in ACUITY Trial

The number of patients in the ATP (as-treated) population is shown in the table below.

Table 8: Numbers of patients evaluable for safety in the ACUITY trial - ATP population

	Enoxaparin/UFH N=4697						Bivalirudin N=9025					
Category	**+ GPI [a] N=3603, n (%)**		**Alone [b] N=1094, n (%)**		**Total N=4697, n (%)**		**+ GPI [a] N=3849, n (%)**		**Alone [b] N=5176, n (%)**		**Total N=9025, n (%)**	
Received any GPI	3603	(100)	0	(0.0)	3603	(76.7)	3849	(100)	0	(0.0)	3849	(42.6)
Procedure (revascularisation/clinical procedure): [c]												
PCI	2536	(70.4)	80	(7.3)	2616	(55.7)	2838	(73.7)	2322	(44.9)	5160	(57.2)
CABG	303	(8.4)	263	(24.0)	566	(12.1)	273	(7.1)	697	(13.5)	970	(10.7)
MM	764	(21.2)	751	(68.6)	1515	(32.3)	738	(19.2)	2157	(41.7)	2895	(32.1)

Percentages are calculated based on the number of ATP patients in the corresponding treatment group.

[a] Numbers of patients who received one or more dose of GPI postrandomisation, irrespective of randomisation or reason for GPI administration. The majority of these patients underwent PCI. The bivalirudin + GPI group includes patients randomised to bivalirudin alone who received nonrandomised GPI to manage breakthrough ischaemia (see *Summary of Clinical Efficacy*).

[b] Number of patients who did not receive any GPI postrandomisation, irrespective of randomisation.

[c] Following index angiography, all patients underwent angiographic triage to medical management, PCI, or CABG per local practice. Because a patient may have undergone more than one revascularisation procedure, or may have undergone a revascularisation procedure in addition to medical management, an algorithm was used to assign only one procedure to each patient in the database (hereafter, the procedure determined by the algorithm is referred to as actual procedure). More information is provided in *ACUITY CSR Appendix 16.1.4*.

MM: medical management.

The dose of bivalirudin and the duration of administration are shown in table 9 below. Most patients in ACUITY received additional bivalirudin after the triage decision.

Table 9: Overall exposure to bivalirudin, by study

Study	No. patients exposed	Bolus dose (mg/kg)	IV infusion dose (mg/kg/h)	Median duration of infusion (h)
ACUITY (up to triage decision) [a]	9025	0.1	0.25	4.1
TIMI 7	160	–	0.02	72
	81	–	0.25	72
	88	–	0.5	72
	81	–	1.0	72
TIMI 8	67	0.1	0.25 [b]	72

[a] Number of patients who received bivalirudin as their first study drug postrandomisation. The doses shown are the median values for the average bolus and infusion doses administered up to the triage decision. Patients in the ACUITY trial may have received additional bolus and/or infusion doses of bivalirudin after the triage decision. The median overall duration of the bivalirudin infusion in the ACUITY trial was 6.4 hours.

[b] In the TIMI 8 trial, the bivalirudin dose could be adjusted.

Bleeding

TIMI-defined as intracranial bleeding or bleeding associated with haemoglobin decrease of >5 g/dl (or a haematocrit decrease of 15%).

The main safety endpoint was major bleeding measured as per the ACUITY scale, which comprised the following non-CABG bleeding events:

- Intracranial
- Retroperitoneal
- Intraocular
- Access site haemorrhage requiring radiological or surgical intervention
- ≥ 5 cm diameter haematoma at puncture site
- Decrease in haemoglobin concentration of ≥4 g/dl, without an overt bleeding source or >3g/dl with an overt bleeding source.
- Reoperation for bleeding
- Use of any blood product transfusion

The major bleeding results as per the ACUITY scale are shown in tables 10 and 11 below.

Table 10: Incidence of ACUITY-scale major bleeding at the Day 30 visit: Arm C (bivalirudin alone) vs Arm A (heparins + GPI) - ITT population

Bleeding component	Heparins + GPI (A) N=4603, n (%)		Bivalirudin alone (C) N=4612, n (%)		p-value [b]
ACUITY-scale major bleeding [a]	262	(5.7)	139	(3.0)	<0.0001
Intracranial	3	(0.1)	3	(0.1)	0.9981
Retroperitoneal	24	(0.5)	7	(0.2)	0.0022
Intraocular	0	(0.0)	0	(0.0)	nc
Access site haemorrhage	24	(0.5)	14	(0.3)	0.1028
Haematoma ≥5 cm at puncture site	102	(2.2)	32	(0.7)	<0.0001
Decrease in haemoglobin ≥4 g/dl without overt bleeding source	39	(0.8)	33	(0.7)	0.4726
Decrease in haemoglobin ≥3 g/dl with overt bleeding source	102	(2.2)	45	(1.0)	<0.0001
Reoperation for bleeding	2	(0.0)	4	(0.1)	0.4154
Any blood product transfusion	125	(2.7)	75	(1.6)	0.0003

[a] Protocol non-CABG major bleeding. Numbers of patients with individual bleeding components do not add to total, as patients may have experienced more than one bleeding event.
[b] Chi-square test of difference between treatments.
nc: not calculated

The above results show a clear and statistically significant reduction in major bleeding in favour of the bivalirudin alone arm. This result is mostly driven by the significant reductions in haematoma, decrease in Hb>3g/dl and the use of any blood product transfusion.

Table 11: Incidence of ACUITY-scale major bleeding at the Day 30 visit: Arm B (bivalirudin + GPI) versus Arm A (heparins + GPI) - ITT population

Bleeding component	Heparins + GPI (A) N=4603, n (%)		Bivalirudin + GPI (B) N=4604, n (%)		p-value [b]
ACUITY-scale major bleeding [a]	262	(5.7)	243	(5.3)	0.3831
Intracranial	3	(0.1)	3	(0.1)	0.9998
Retroperitoneal	24	(0.5)	26	(0.6)	0.7773
Intraocular	0	(0.0)	2	(0.0)	0.1573
Access site haemorrhage	24	(0.5)	28	(0.6)	0.5786
Haematoma ≥5 cm at puncture site	102	(2.2)	101	(2.2)	0.9422
Decrease in haemoglobin ≥4 g/dl without overt bleeding source	39	(0.8)	33	(0.7)	0.4772
Decrease in haemoglobin ≥3 g/dl with overt bleeding source	102	(2.2)	83	(1.8)	0.1578
Reoperation for bleeding	2	(0.0)	5	(0.1)	0.2568
Any blood product transfusion	125	(2.7)	119	(2.6)	0.6958

[a] Protocol non-CABG major bleeding. Numbers of patients with individual bleeding components do not add to total, as patients may have experienced more than one bleeding event.
[b] Chi-square test of difference between treatments.

There was no difference between the two groups. Of note, there were 2 cases of intraocular bleed in bivalirudin + GPI group but none in Heparin + GPI group.

Results for minor bleeding events also significantly favoured the bivalirudin alone group and were as follows:

	Arm A	Arm B	Arm C
ACUITY non-CABG minor bleeding	993 (21.6%)	1001 (21.7%)	592 (12.8%)

As specified in the protocol and requested by CHMP, bleeding rates were also assessed using the TIMI criteria (Rao *et al*, 1988), which are independent of CABG bleeding.
TIMI major bleeding was defined as any one of the following:

- Intracranial
- Decrease in haemoglobin concentration ≥ 5 g/dl

TIMI minor bleeding was defined as any one of the following:

- Haematuria or haematemesis
- Decrease in haemoglobin concentration ≥4 g/dl without an overt source of bleeding
- Decrease in haemoglobin concentration of ≥3 g/dl with an overt source of bleeding

The major bleeding results as per the TIMI scale are shown in tables 12 and 13 below.

Table 12: Incidence of TIMI major and minor bleeding at the Day 30: Arm C (bivalirudin alone) versus Arm A (heparins + GPI) - ITT population

TIMI bleeding endpoint	*Heparins + GPI (A) N=4603, n (%)*	*Bivalirudin alone (C) N=4612, n (%)*	*Diff. C – A*	*95% CI*
TIMI major bleeding	*86 (1.9)*	*43 (0.9)*	*– 0.0094*	*(–0.0142, –0.0046) **
TIMI minor bleeding	*295 (6.4)*	*170 (3.7)*	*– 0.0272*	*(–0.0362, –0.0183) **

Numbers of patients with individual bleeding components do not add to total, as patients may have experienced more than one bleeding event.

** indicates that the risk difference between heparins + GPI and bivalirudin alone is significantly different from zero.*

Table 13: Incidence of TIMI major and minor bleeding at the Day 30: Arm B (bivalirudin + GPI) vs Arm A (heparins + GPI) - ITT population

TIMI bleeding endpoint	*Heparins + GPI (A) N=4603, n (%)*	*Bivalirudin + GPI (B) N=4604, n (%)*	*Diff. B – A*	*95% CI*
TIMI major bleeding	*86 (1.9)*	*76 (1.7)*	*– 0.0022*	*(–0.0075, 0.0032)*
TIMI minor bleeding	*295 (6.4)*	*281 (6.1)*	*– 0.0031*	*(–0.0129, 0.0068)*

Numbers of patients with individual bleeding components do not add to total, as patients may have experienced more than one bleeding event.

According to the TIMI bleeding criteria, the absolute difference in major bleeding between the two GPI strategies and bivalirudin monotherapy narrowed to 1% or less (1.7%-1.9% vs 0.9%).

Overall bleeding

Overall bleeding frequency at Day 30 at different bleeding sites is presented below.

Table 14: 30-day bleeding site frequency data (bivalirudin ± GPI vs heparin + GPI inhibitor); ITT population.

Bleeding site	**Bivalirudin ±GPI (N=9025) %**	**Heparin +GPI (N=4697) %**
Puncture site haematoma > 5 cm	6.0	7.4
Oozing blood at puncture site	5.7	8.3
Ecchymosis	4.8	5.6
Epistaxis	1.3	1.4
Gingival Bleeding	0.9	0.6
Genitourinary	0.7	0.8
Gastrointestinal	0.6	0.9
Sheath puncture site	0.5	0.5
Retroperitoneal	0.4	0.5
Haemoptysis	0.3	0.3
Melena	0.3	0.4
Ear, Nose or Throat	0.1	0.1
Cardio/pulmonary	<0.1	0.1
Intracranial	<0.1	<0.1
Other	3.0	4.3

Major bleeding occurred most frequently at the sheath puncture site. Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included "other" puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.

Post-hoc bleeding analyses

Further to a request from CHMP, the Applicant carried out a number of additional analyses of the bleeding data.

To ensure that ACUITY-scale bleeding outcomes were not overly influenced by haematomas ≥5cm, additional analyses were performed to examine outcomes when these haematomas were excluded.

Table 15: 30 day bleeding outcomes in ACUITY

	Heparins + GPI (ASA + Thieno) N = 4603	Bivalirudin + GPI (ASA + Thieno) N = 4604	Bivalirudin (ASA + Thieno) N = 4612
	ACUITY Scale		
ACUITY non-CABG major bleeding	262 (5.7%)	243 (5.3%)	139 (3.0%)
ACUITY non-CABG major bleeding excluding haematomas ≥5cm	208 (4.5%)	187 (4.1%)	124 (2.7%)

As detailed in the table 15 above, a 40% reduction in ACUITY scale major bleeding was seen, comparing Arm A to Arm C, when large haematomas were excluded.

Given that bleeding is more of a problem in interventions through the femoral route rather than the brachial route, the Applicant was asked to carry out further analyses according to the route of angiography used. However, ACUITY was not designed or powered to provide such analyses. The ACUITY trial demonstrated comparable ischaemic outcomes for femoral versus radial access at 1 year (see table 16) and a comparable reduction in organ bleeding irrespective of the route of angiographic access (see table 17).

Table 16: 1-year outcomes, by angiographic access site, in the ACUITY trial

	Femoral	Radial	p-value
Composite ischaemia	15.4%	15.0%	0.76
Death	3.6%	4.0%	0.60
MI	6.9%	7.4%	0.59
Unplanned revascularisation for Ischaemia	8.4%	6.9%	0.13

Table 17: 30 Day organ bleeds*, by arm, in the ACUITY trial

	Heparin + GPI	Bivalirudin + GPI	Bivalirudin alone
Both Radial and Femoral	7.3%	7.2%	4.2%
Radial	7.4%	9.7%	4.7%
Femoral	7.3%	7.1%	4.1%

*Organ bleeding defined as intracranial, intraocular, gastrointestinal, genitourinary, pulmonary, ear nose and throat, pericardial.

The Cardiovascular Scientific Advisory Group (SAG CVS) concluded that the findings from ACUITY are applicable independent of access route and that no particular benefit or risk is associated with the product when a particular access route is used.

Another analysis performed on ACUITY evaluated bleeding in patients receiving consistent UFH or enoxaparin + GPI (n=2137) versus patients switched from either heparin based therapy to bivalirudin monotherapy at the time of randomisation (n=2078). In line with the overall trial, patients switched to bivalirudin had significantly fewer major bleeding events (2.8% vs 5.8%, RR 0.49 [0.36 -0.66], p < 0.01), with similar incidence of composite ischaemia (6.9% vs 7.4%, RR 0.93 [0.75-1.16], p=0.52) to those maintained on consistent therapy. These results also persisted in the cohort of patients with elevated cardiac biomarkers or ECG changes at presentation as well as in patients undergoing PCI.

Discussion on bleeding events
No difference was observed in bleeding events at 30 days between bivalirudin + GPI vs Heparin + GPI. However, there was a significant difference in favour of bivalirudin alone when compared with heparin + GPI, suggesting a significant role of GPI in the observed bleeding events. The bleeding advantage seen at 30 days persists at 1 year with or without use of TIMI scale. This significant difference was also noted when using the TIMI scale, which approached 1%. This absolute reduction in bleeding is clinically meaningful. TIMI major bleeds have been shown to be highly predictive of 1 year mortality, with a hazard ratio of 3.60. Further evidence of the importance of avoiding TIMI-scale major bleeds is the high associated rate of blood transfusions

According to the MAH, by using bivalirudin, 9 TIMI major bleeds per 1000 patients treated could be avoided. In comparison, at 30 days there is the possibility of an excess of 5 MIs per 1000 patients treated and at 1 year there is the risk of 8 MIs per 1000 patients treated.

Other Adverse Events (AEs) and deaths
Approximately 23.3% of patients receiving bivalirudin experienced at least one adverse event and 2.1% experienced an adverse drug reaction. Adverse event reactions are listed by system organ class in Table 18.

Table 18. ACUITY trial; overall adverse drug reaction data

System organ class	**Very Common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to ≤1/100)	**Rare** ≥1/10,000 to ≤1/1,000
Blood and the lymphatic system disorders			INR increased, Thrombocytopenia, anaemia.	
Immune system disorders			Hypersensitivity	
Nervous system disorders			Headache	
Cardiac disorders				Bradycardia
Vascular disorders	Minor bleeding	Major bleeding	Haematoma, hypotension	Haemorrhage, Vascular pseudoaneurysm
Gastrointestinal disorders			Nausea, vomiting	
Skin and subcutaneous tissue disorders				Rash, urticaria
Musculoskeletal and connective tissue disorders			Back pain, chest pain, Groin pain	
General disorders and administration site conditions				Injection site reactions

The AE profile of bivalirudin in patients with ACS did not show any new safety signal. Few patients in these studies experienced allergic/immunologic/hypersensitivity AEs, and the frequencies were generally balanced between treatment groups. No deaths were reported due to these events. The incidence of AEs were similar across treatment groups in ACUITY as well as in other ACS studies. Of note, more bivalirudin than enoxaparin/UFH patients experienced adverse events related to gastrointestinal SOC (5.0% vs 4.3%).

Regarding other events of special interest, the overall incidence of *thrombocytopaenia* in ACUITY trial was 11% and was comparable in the overall enoxaparin/UFH and bivalirudin groups. It was reported in 10 bivalirudin-treated patients (0.1%). The majority of these patients received concomitant ASA and clopidogrel, and 6 out of the 10 patients also received a GPI. There were no reports of mortality among these patients.

Regarding deaths, the heparin and bivalirudin groups were well balanced with respect to the percentage of patients who died. Most frequently reported SAEs with an outcome of death were cardiac arrest, cardiogenic shock, and myocardial infarction. In the ACUITY trial, 69 (1.5%) enoxaparin/UFH and 136 (1.5%) bivalirudin patients in the ATP population experienced one or more

SAE with an outcome of death up to Day 30 visit. Mortality by a major bleeding event was reported in 5.6% of enoxaparin/UFH and 5.0% of bivalirudin patients up to Day 30 visit.

Pharmacovigilance

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan. The Summary table of the RMP can be found at the end of this report.

Exposure to bivalirudin in additional ACS patients resulting from approval of this indication will be at levels of drug lower than those previously evaluated and should offer no additional safety concerns and for durations of treatment which have previously been studied or observed.

The ImproveR study, designed to evaluate the use of Angiox in routine European clinical practice, identified the misadministration practice of bolus only dosing. Single bolus doses potentially lead to sub-therapeutic doses. The clinical consequences of administering a sub-therapeutic dose of a procedural anticoagulant are potentially serious.

The MAH has been working with the National Agencies and the Pharmacovigilance Working Party to address the concerns raised. The risk minimisation activities proposed to curtail the use of bolus only dosing are the following:

1. A direct healthcare professional communication (circulated on 29 October 2007)
2. Investigations into physician attitudes and practices
3. Review of promotional and educational materials
4. Sales representative training
5. Changes to the SmPC for Angiox

As a follow up measure, the MAH should propose tools to assess the effectiveness of these measures in the next RMP update.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Pharmacovigilance Plan

This is entirely based on spontaneous reporting. With regards to serious bleeding reactions and serious immunological reactions received in the EU, the company should continue to actively follow up these for further information as this will aid assessment of these cases. The company has been actively monitoring these issues in their PSURs for Angiox indicated for PCI and this should be continued.

The CHMP considered that due to the likely increase in use following the extension of indication, there is an argument for drug utilisation studies, which would obviously need to be entirely hospital-based. Therefore, as a follow up measure the company is requested to conduct a drug utilisation study and provide a protocol with timelines for completion of the study.

Discussion

This request for a new indication for the treatment of adult patients with acute coronary syndromes (UA/NSTEMI) is supported by data from a single pivotal study (ACUITY) and two smaller supportive studies (TIMI 7 & TIMI 8). All the clinical trials were carried out in conformity with the ethical requirements and principles of Good Clinical Practice in force at the time the studies were performed. Only ACUITY will be discussed.

ACUITY was an open-label, non-inferiority trial comparing bivalirudin with heparin (UFH or enoxaparin) in medium to high risk ACS patients without ST-segment elevation undergoing early

invasive management and evaluating the clinical impact of a treatment strategy based on the timing of GPI initiation. The SAG CVS agreed that it was a pragmatic trial, reflecting current practice. Indeed, based on the ESC recommendation that GPIs should be used in high risk patients with ACS, the use of these agents in the ACUITY trial population is considered appropriate and consistent with ESC guidelines and current suggested European clinical practice.

One of the initial points raised by CHMP was the open-label nature of the trial. The MAH argues that the complexities involved in the clinical management of patients with ACS did not allow a double-blind approach to masking the identities of study treatments or the timing of GPI initiation. Therefore, a number of strategies were used to minimise bias pertaining to the reporting of the different endpoints, especially MIs and revascularisation events (see page **), and the review by the blinded CEC of all pertinent source documentation. To avoid potential bias in the reporting of MI, definitions of MI were carefully and prospectively defined. Measurements used to quantify MI were standardised and all MI events were independently adjudicated by a blinded CEC. The SAG CVS and the CHMP agree that it is unlikely that the open-label nature of the trial had an undue influence on the results.

Efficacy

The ACUITY trial protocol established three primary endpoints. The CHMP considered that the "net clinical outcome" endpoint, a composite of incidence of all-cause death, MI, unplanned revascularisation for ischaemia, or major bleeding, was difficult to evaluate and unacceptable, given the mix of efficacy outcomes with the well established safety measure of bleeds. The CHMP strongly believes that the primary endpoint should only include efficacy variables and safety variables should be evaluated separately in order to avoid drawing false conclusions on efficacy. This concern was shared by the SAG CVS and the results of this endpoint have not been considered in the evaluation of this new indication, nor have they been reflected in the SPC. Similarly, the bleeding results are considered a safety outcome and are accordingly discussed in the safety section of this report.

The main efficacy discussion centred on the results of the composite ischaemic endpoint and its individual components. Whilst the CHMP agreed that the results of the two bivalirudin arms were statistically non-inferior to the control heparin group, the data at 30 days, defined as the primary outcome measure, showed a worrying numerical increase in mortality and MI notably in the "bivalirudin alone" group. Moreover, the Committee also questioned the rather wide pre-specified relative non-inferiority margin of 25%. The MAH claimed that this margin was considered acceptable by clinicians. Moreover, the confidence intervals of the point estimates were reassuringly tight, with the 1-year results effectively within a relative non-inferiority margin of 15%. Subsequent to the first SAG CVS meeting, the MAH submitted the 1-year data. The results of the two bivalirudin arms were again statistically non-inferior, and, importantly, reassuring since the negative mortality trend was reversed in favour of bivalirudin. Regarding the remaining modest increase in MI, the additional analyses carried out by the MAH at the request of CHMP showed that it was mainly driven by enzymatic MI, and this has to be balanced against the clear bleeding advantage – see later.

Further to the additional analyses requested by CHMP, it was apparent that the results of the composite ischaemic endpoint and its individual components were most favourable to bivalirudin, especially for bivalirudin alone, in patients who had received ASA and clopidogrel. Indeed, the individual trends are reversed. Considering the acknowledged bleeding advantage is maintained in this patient population, the SAG recommended and the CHMP agreed to restrict the use of bivalirudin in ACS patients to those pretreated with ASA and clopidogrel. In addition, it was agreed to further qualify the target population as "high risk" (i.e. scheduled for urgent or early intervention) as this reflected the vast majority of patients included in the ACUITY trial.

Regarding the pre-PCI IV administration of Enoxaparin, which is not approved in the EU although included in the ESC recommendations, the applicant has shown that there was no difference in clinical outcomes between patients who received the additional dose of enoxaparin and those who did not. This has been reflected in section 5.1 of the SPC.

Finally, regarding the results of the ACUITY Timing Trial (the so-called secondary randomisation), there were no significant differences in efficacy outcomes at Day 30 or at 1-year based on the timing

of GPI administration, namely upfront (prior to angiography) or deferred until PCI. There was a reduction in bleeding for bivalirudin monotherapy compared to either GPI timing strategy.

Safety
The main safety discussion centred on the purported bleeding advantage observed in patients treated with bivalirudin alone. The results of the primary safety endpoint (non-CABG major bleeding measured by the ACUITY scale) appeared quite impressive in favour of bivalirudin alone. The CHMP questioned the validity on the non-validated ACUITY scale, particularly several of its components, such as "puncture site haematoma" and access-site bleeding, regarded as being of less clinical importance when compared to the TIMI scale. The SAG CVS acknowledged the higher sensitivity of the ACUITY scale but felt that the bleeding advantage, even for these less critical bleeding events, was significant and should not be disregarded. Although the scale of the difference is smaller when considering the TIMI scale, it was still believed to be clinically significant. Moreover, subsequent analyses performed at the request of CHMP showed that the haematoma event rate has no influence on the bleeding benefit shown for bivalirudin, showing that the ACUITY scale remains discriminatory even after large haematomas are excluded.

The CHMP noted that the patent bleeding advantage of bivalirudin over heparin at 30-days and which persisted at 1 year, both in terms of major and minor bleeding, was only observed in the bivalirudin alone arm (regardless of bleeding scale), suggesting that the significantly higher rates of bleeding observed in the "heparin + GPI" and "bivalirudin + GPI" arms suggest a major role of GPI in the bleeding events. The magnitude of the bleeding difference between the "bivalirudin alone" and the "heparin + GPI" and "bivalirudin + GPI" groups is clearly maintained when considering the subpopulation of patients pre-treated with ASA and clopidogrel.

Another point of debate was whether the route of angiography used should be reflected in the SPC, given that bleeding is more of a problem in interventions through the femoral route rather than the brachial route. Further to subsequent analyses carried out by the MAH, the SAG CVS concluded, and the CHMP agreed, that the ACUITY findings are applicable regardless of access route.

Otherwise, the safety profile of bivalirudin in patients with ACS did not show any new untoward signal. The incidence of adverse events was similar across treatment groups in ACUITY as well as in other ACS studies Few patients experienced allergic/immunologic/hypersensitivity events, and the frequencies were generally balanced between treatment groups.

Regarding other events of special interest, the overall incidence of *thrombocytopaenia* in ACUITY trial was comparable in the overall enoxaparin/UFH and bivalirudin groups.

Finally, the MAH has taken the opportunity to update section 4.9 of the SPC (*Potential for Overdose*) in order to reflect the experience with cases of overdose of up to 10 times the recommended dose reported in clinical trials. None of these cases were associated with bleeding or other adverse events.

Evaluation of Benefit – risk balance

The use of bivalirudin is associated with a favourable benefit/risk profile. Despite a numerical difference in deaths at 30 days and of MI at 30 days and 1 year, these differences were not statistically significant; in fact, mortality favoured bivalirudin at 1 year. In contrast, the bleeding differences observed in patients treated with bivalirudin were statistically and clinically significant and were maintained regardless of the bleeding scale employed.

It may be concluded that bivalirudin is an acceptable substitute for heparin (either UFH or enoxaparin) when used with dual antiplatelet therapy - aspirin and clopidogrel.

Summary Table of the Risk Management Plan (version 4)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk management activities (routine and additional)
Identified risk: Bleeding events	Expedited reporting of bleeding events. Active surveillance of major bleeding events including the use of follow-up questionnaires to ensure high quality and complete information. Inclusion of discussion of medically important bleeding and serious immunologic events in the PSUR. Routine pharmacovigilance activities.	Routine measures only. Identified risks with respect to bleeding are considered well described in current labelling (see below), are responsive to aggressive surveillance and communication, and are unlikely to benefit from additional measures. Section 4.3: Angiox is contraindicated in patients with active bleeding or increased risk of bleeding because of haemostasis disorders and/or irreversible coagulation disorders Section 4.5: From the knowledge of their mechanism of action, combined use of anti-coagulant medicinal products (heparin, warfarin, thrombolytics or antiplatelet agents) can be expected to increase the risk of bleeding. In any case, when bivalirudin is combined with a platelet inhibitor or an anticoagulant drug, clinical and biological parameters of haemostasis should be regularly monitored. Section 4.8: Platelets, bleeding and clotting In ACUITY, bleeding data were collected separately from adverse events. Major bleeding was measured by the ACUITY and TIMI major bleeding scales as defined in the footnotes to Table 2. Minor haemorrhage was defined as any observed bleeding event that did not meet the criteria for a major haemorrhage. Minor bleeding occurred very commonly (≥ 1/10) and major bleeding occurred commonly (≥1/100 and <1/10). Both minor and major bleeds were significantly less frequent with bivalirudin alone than the heparin plus GPIIb/IIIa inhibitor and bivalirudin plus GPIIb/IIIa inhibitor groups (see Table 2). Similar reductions in bleeding were observed in patients who were switched to bivalirudin from heparin-based therapies (N = 2078). Major bleeding occurred most frequently at the sheath puncture site (see Table 3). Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included “other” puncture site, retroperitoneal, gastrointestinal, ear, nose or throat. Section 4.9: Cases of overdose of up to 10 times the recommended dose have been reported in clinical trials. Single bolus doses of bivalirudin up to 7.5mg/kg have also been reported. None of these cases were associated with bleeding or other adverse events. In cases of overdose, treatment with bivalirudin should be immediately discontinued and the patient monitored closely for signs of bleeding. In the event of major bleeding, treatment with bivalirudin should be immediately discontinued. There is no known antidote to bivalirudin, however, bivalirudin is haemo-dialysable. Section 5.1:

		The incidence of both ACUITY-scale and TIMI-scale bleeding events up to day 30 is presented in Table 9 for the overall (ITT) population and for patients that received aspirin and clopidogrel as per protocol.
Identified risk: Serious immunological events	Expedited reporting of serious immunological events. Active surveillance of serious immunological events including the use of follow-up questionnaires to ensure high quality and complete information. Inclusion of discussion of serious immunological events in the PSUR. Routine pharmacovigilance activities.	Routine measures only. Identified risks with respect to immunological reaction are considered well described in current labelling (see below) are responsive to aggressive surveillance and communication, and are unlikely to benefit from additional measures. Section 4.4 Hypersensitivity: Allergic type hypersensitivity reactions were reported uncommonly in clinical trials. Necessary preparations should be made to deal with this. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of chest, wheezing, hypotension and anaphylaxis. In the case of shock, the current medical standards for shock treatment should be applied. Anaphylaxis, including anaphylactic shock with fatal outcome has been reported very rarely in post-marketing experience (see section 4.8). Treatment-emergent positive bivalirudin antibodies are rare and have not been associated with clinical evidence of allergic or anaphylactic reactions. Caution should be exercised in patients previously treated with lepirudin who had developed lepirudin antibodies. Section 4.8 See Tables 1, 4 & 6.
Identified risk: Medication errors	Continue routine pharmacovigilance procedures for events describing medication errors. Implement additional pharmacovigilance measures for events describing bolus only dosing: Perform active follow up of adverse events where bolus only dosing is reported. Routine pharmacovigilance activities. Conduct a drug utilization study to obtain information on the use and dose patterns of Angiox in European clinical practice.	Update section 4.2 of Angiox® SmPC with additional wording regarding the importance of the use of the bolus and infusion dose (even for short PCI procedures). Section 4.2: The safety and efficacy of a bolus only dose of Angiox has not been evaluated and is not recommended even if a short PCI procedure is planned DHCP Communication: To provide a direct reminder to the interventional cardiology community of the importance of using the approved regimen for Angiox® (DHCP circulated 29th October 2007).
Potential risk: INR increase following co-administration of warfarin and bivalirudin	Continue to closely monitor events describing these reactions.	Potential risks with respect INR increase are considered adequately described in current labelling (see below) are responsive to surveillance and are unlikely to benefit from additional measures at this time. Sections 4.5 From the knowledge of their mechanism of action, combined use of anti-coagulant medicinal products (heparin, warfarin, thrombolytics or antiplatelet agents) can be expected to increase the risk of bleeding. In any case, when bivalirudin is combined with a platelet inhibitor or an anticoagulant drug, clinical and biological parameters of haemostasis should be regularly monitored. Section 5.1 In healthy volunteers and patients, bivalirudin exhibits dose- and concentration dependent anticoagulant activity as evidenced as prolongation of the ACT, aPTT, PT, INR and TT. Intravenous administration of bivalirudin

		produces measurable anticoagulation within minutes.
Potential risk: Adverse reactions leading to cardiac arrest	Continue to closely monitor events describing these reactions. Regular review of MedDRA preferred term/TME 'cardiac arrest'.	Potential risks with respect to events leading to cardiac arrest are considered adequately described in current labelling (see below) are responsive to surveillance and are unlikely to benefit from additional measures at this time. Section 4.8: Tables 4 & 6. Section 5.1 Tables 7, 8 and 10
Potential risk: Thrombocytopenia with bivalirudin given concomitantly with inhibitors of platelet aggregation	Continue to closely monitor events describing these reactions.	Potential risks with respect thrombocytopaenia with bivalirudin when given concomitantly with inhibitors of platelet aggregation are considered adequately described in current labelling (see below) are responsive to surveillance and are unlikely to benefit from additional measures at this time. Section 4.8: Thrombocytopenia was reported in 10 bivalirudin-treated patients participating in the ACUITY study (0.1%). The majority of these patients received concomitant acetylsalicylic acid and clopidogrel, and 6 out of the 10 patients also received a GPIIb/IIIa inhibitor. Mortality among these patients was nil.
Important Missing Information	Ongoing AE report surveillance for pregnant and lactating patients. Ongoing AE report surveillance for indications and clinical circumstances of AEs in paediatric patients.	Relatively little exposure in these two key patient groups has occurred. Ongoing surveillance and report analysis is regarded as the most effective way to obtain AE data in these patients.