

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

mg/kg) in patients with coronary artery disease and undergoing elective PCI pretreated with sc enoxaparin (30 mg iv bolus and 1 mg/kg sc or minimum 5 sc injections to be at steady state) and taken to the cardiac catheterization laboratory 8 to 12 hours after their last sc dose. Minimum and maximum values of anti-Xa activities were of  $0.94 \pm 0.24$  and  $1.16 \pm 0.24$  IU/mL, respectively, between 2 and 8 hours after the last sc dose and with all values above 0.6 IU/mL (except one: 0.578 IU/mL). These anti-Xa levels were in the range similar to those achieved in the Collet study<sup>29</sup>, which showed that the efficacy and safety was good for PCI within the 8 hours post sc administration of enoxaparin.

Based on the above data, the ExTRACT protocol required that

- (i) if the last sc administration was given  $\geq 8$  hours before balloon inflation, patients undergoing PCI receive an iv bolus of enoxaparin 0.3 mg/kg, and
- (ii) if the last sc administration of enoxaparin was given  $< 8$  hours before inflation, no additional dosing was required. (Please also see Section 10 Appendix, 10.1 Review of individual study reports).

## 8.2 Drug-Drug Interactions

The sponsor submitted that no specific drug interaction studies were conducted for this submission.

## 8.3 Special Populations

**Elderly patients:** Please see dose adaptation for elderly patients in Section 8.1 above.

**Renal impairment:** Please see dose adaptation for patients with impaired renal function in Section 8.1 above.

**Pregnancy and Lactation:** The sponsor submitted that a total of 1800 cases of drug exposure during pregnancy and lactation were recorded from the first marketing authorization up to May 2006 in the Sanofi-Aventis post-marketing global pharmacovigilance database, and that, as there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

While it was shown in rat studies that enoxaparin and/or its metabolites are excreted in milk, it is not known whether enoxaparin is excreted in human milk.

## 8.4 Pediatrics

In compliance with the 63 FR 66670 and in accordance with the draft guidance, the Sponsor submitted a request for a full waiver (all pediatric age groups) of the pediatric study requirements to the Division of Medical Imaging and Hematology products, where

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

the original IND 31,532 resides, as specified in 21 CFR 314.55(c) for enoxaparin in the indication of STEMI.

The justification for the enoxaparin pediatric waiver for the indication of STEMI is as follows:

(1) Substantial number of pediatric patients:

As defined in 63 FR 66670, the cut-off for a substantial number of pediatric patients is 50,000 pediatric patients with the disease or condition for which the drug is indicated. Recent data taken from the 2003 National Hospital Discharge Survey (NHDS; July 8, 2005) provided no data for patients under the age of 15 for acute myocardial infarction, coronary atherosclerosis or other ischemic heart disease, but only a footnote indicating that such data do not meet standards of reliability or precision (i.e., < 30 records in the sample or a relative standard error >30%.) The data reported incidence rates as low as 1.2 per 10,000 (cardiac dysrhythmia), suggesting that the number of pediatric patients with STEMI is even smaller and well below the 50,000 patient cut-off.

(2) Meaningful therapeutic benefit:

The rare pediatric patients with atherosclerosis (and the potential for acute MI) are currently treated with HMG-CoA reductase inhibitors to lower lipid levels in response to the underlying etiology of their disease. Enoxaparin's known mechanism of action does not support a meaningful therapeutic benefit on this basis.

By letter dated 24-Jul-2006, the Division of Medical Imaging and Hematology products, granted a waiver for pediatric studies under section 2 of the Pediatric Research Equity Act.

## 8.5 Advisory Committee Meeting

Not applicable.

## 8.6 Literature Review

Reperfusion therapy is the standard of care for patients with STEMI. The therapeutic approach has dramatically improved the prognosis of patients with STEMI over the last decade<sup>2,3</sup>. However, the current practice of using fibrinolytics, ASA, and antithrombin (iv UFH) still results in at least a 10% rate of death or re-infarction within 1 month following treatment<sup>2,4,5,6,7,8,9</sup>.

### Fibrinolytic therapy

Depending on the fibrinolytic agent prescribed, patency of the infarct-related artery (IRA) is established by 90 minutes in only 60% to 80% of patients and full antegrade perfusion (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow) is achieved in only 30% to 55% of patients<sup>31,32</sup>. This is particularly important because the relationship between full patency and survival is quite strong<sup>33</sup>. Reopening of the occluded artery minimizes myocardial injury, preserves cardiac function, and ultimately improves overall survival.

An overview<sup>34</sup> from 9 trials of fibrinolytic therapy (vs control) for STEMI has shown a

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

highly significant 18% relative reduction in 35-day mortality (9.6% fibrinolysis vs 11.5% control) which corresponds to a reduction of 18 deaths per 1000 patients treated when data from all patient groups are pooled. The survival benefit is maintained over the long term up to 10 years. Patients with new left bundle-branch block, anterior infarction and the greatest area of risk (the number of ECG leads affected and the extent of ST deviation, derived maximal benefit from fibrinolytic therapy<sup>34</sup>.

A limitation of fibrinolysis is due to re-occlusion of the IRA after initial successful fibrinolysis in approximately 5% to 10% of patients<sup>35,36</sup>. The risk of re-occlusion appears to be related to the underlying degree of stenosis, as well as residual thrombus<sup>37,38,39</sup>. When re-occlusion occurs, it may be associated with recurrent infarction and an increased risk of mortality, morbidity, and poor ventricular function<sup>40</sup>.

### Percutaneous Coronary Intervention (PCI)

Primary PCI: In 22 randomized clinical trials comparing Primary PCI with fibrinolytic therapy<sup>41</sup>, PCI-treated patients experience lower short-term mortality rates (5.0% vs 7.0%, RR 0.70, 95% CI 0.58 to 0.85,  $p = 0.0002$ ), less nonfatal reinfarction (3.0% vs 7.0%, RR 0.35, 95% CI 0.27 to 0.45,  $p = 0.0003$ ), and less hemorrhagic stroke (0.05% vs 1.0%, RR 0.05, 95% CI 0.006 to 0.35,  $p = 0.0001$ ) than those treated by fibrinolysis but with an increased risk for major bleeding (7.0% vs 5.0%, RR 1.3, CI 1.02 to 1.65,  $p = 0.032$ ).

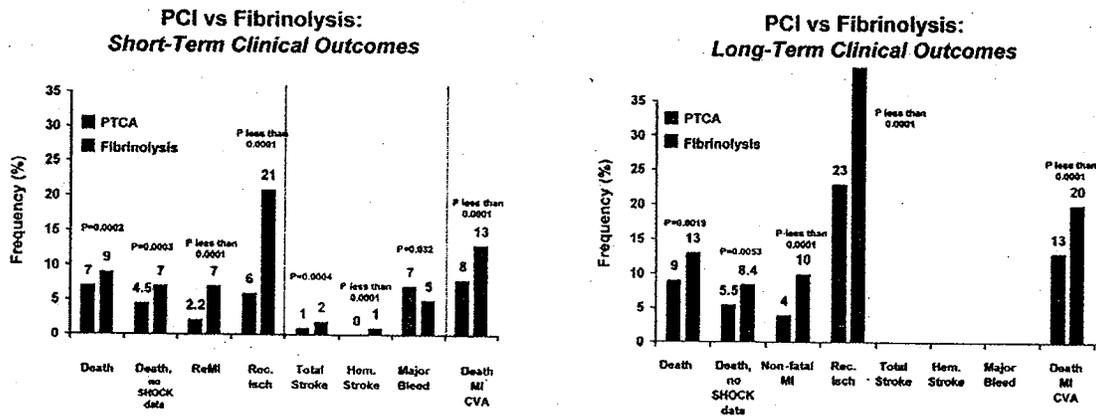


Figure 16 PCI vs fibrinolysis for STEMI: short- (4-6 wks) and long-term outcomes in 23 trials (N=7739)

PTCA= percutaneous transluminal coronary angioplasty, MI= myocardial infarction, ReMI= recurrent MI, Res Isch= recurrent ischemia, Hem. Stoke= hemorrhagic stroke, CVA= cerebrovascular accident. (From Kelly et al, Lancet 2003; 361: 13-20)<sup>41</sup>.

Primary PCI appears to have its greatest mortality benefit over fibrinolysis in high-risk patients: (i) in patients with cardiogenic shock (an absolute 9% reduction in 30-day mortality), (ii) in patients with CHF (a 33% relative risk reduction with primary PCI vs a 9% relative risk reduction with fibrinolytic therapy), and (iii) in patients with anterior STEMI (reduced mortality); but there is no difference in patients with non-anterior STEMI.

Rescue PCI (PCI within 12 hours after failed fibrinolysis for patients with continuing ischemia): While iv fibrinolytic therapy successfully restores coronary TIMI 2/3 flow at 90 minutes in 50% to 85% of patients with STEMI, in those in whom fibrinolysis is unsuccessful, antegrade coronary flow can be restored with PCI, providing an improved long-term outcome. The Randomized Evaluation of Rescue PCI with Combined

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

Utilization End Points (RESCUE) trial<sup>42</sup> demonstrated a reduction in rates of in-hospital death and a combined end point of death and CHF that was maintained up to 1 year after study entry for patients presenting with anterior STEMI who failed fibrinolytic therapy, when PCI was performed within 8 hours after the onset of symptoms.

***PCI for cardiogenic shock:*** Two small randomized clinical trials (the SHOCK trial and the SMASH trial) showed a statistically insignificant but clinically important absolute 9% reduction in 30-day mortality<sup>1</sup>.

***Facilitated PCI:*** This uses pharmacologic therapy to open the artery on the way to the catheterization laboratory. The ASSENT-4 trial<sup>43</sup> comparing pretreatment with full-dose TNK in patients with STEMI referred for PCI vs PCI alone showed **worse 30-day mortality** (6.0% in patients pre-treated with TNK vs 3.8% in those receiving PCI alone,  $p=0.04$ ), **more than double rates of reinfarction** (4.1% vs 1.9%,  $p=0.01$ ), and **20 times higher abrupt vessel closure** (1.9% vs 0.1%,  $p<0.001$ ).

Use of half-dose fibrinolytic therapy with GPIIb/IIIa inhibition prior to PCI in the ADVANCE MI trial<sup>44</sup> and the BRAVE trial<sup>45</sup> also did **not** show reduction in infarct size, and **showed higher rates of death or heart failure, and larger number of major hemorrhages.**

On the other hand, the open-label, phase 4 TITAN-TIMI 34 trial<sup>46</sup>, where 343 STEMI patients undergoing primary PCI were randomized to receive **eptifibatide** early or later, showed that early treatment with eptifibatide in the emergency department before PCI produced statistically significant ( $p=0.049$ ) faster blood flow through the blocked artery.

### ***Aspirin (ASA)***

The use of ASA has been shown to be effective for those patients ineligible to receive thrombolytic therapy or PCI, due to either inaccessibility to treatment, a negative balance between risk and clinical benefit, or contraindications related to comorbid disease.

However, patients who do not receive reperfusion therapy are at higher risk for future adverse events<sup>3</sup>.

### ***Antithrombin therapy***

The current ACC/AHA guidelines<sup>1</sup> and European Society of Cardiology (ESC) guidelines<sup>47</sup> for the management of STEMI recommend iv UFH for patients treated with alteplase or more fibrin-specific thrombolytic agents<sup>47</sup>.

#### ***(1) Does intravenous UFH provide a benefit (prevention of death or reinfarction) in patients with STEMI (who are routinely treated with aspirin and thrombolysis)?***

A fairly recent meta-analysis of randomized trials in patients with STEMI revealed 4 trials of UFH vs no heparin or placebo<sup>23</sup>. Two studies (ISIS-2 Pilot and OSIRIS) used streptokinase, 1 used alteplase and 1 used anistreplase (Table 46). The initial dose of aspirin was  $\geq 200$  mg in all trials, and was followed by a maintenance dose of 75~325 mg/day. The duration of UFH treatment was 1~5 days. Two of these studies were double-blind and placebo-controlled (ECSG and OSIRIS); follow up was complete in the 1 study that reported this (ISIS-2 Pilot).

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

**Table 46 UHF vs no heparin or placebo**

Study	Eligibility	N	Blinding	Thrombolysis	Randomized Treatment			Primary Outcome	Follow up
					UFH*	Control	Aspirin		
ISIS-2 Pilot, 1987 <sup>42</sup>	Suspected MI ≤24 h	209	Open label	SK 1.5 MU over 1 h	No bolus, 1000 IU/h for 48 h†	No heparin	325 mg/d	New MI, death	In-hospital, 1 y (death)
ECSG, 1992 <sup>43</sup>	Age 21-70 y; STEMI, ≤6 h	652	Double-blind	tPA 100 mg over 3 h	5000 IU bolus, 1000 IU/h for 48-120 h	Placebo	300 mg PO or 250 mg IV‡; then 75-125 mg PO Alternate days	Angiographic patency	In-hospital
OSIRIS, 1992 <sup>44</sup>	STEMI, ≤6 h	128	Double-blind	SK 1.5 MU over 1 h	10 000 IU bolus, 1000 IU/h for 24 h	Placebo	200 mg/d	Reperfusion, angiographic patency, LVEF	In-hospital
DUCCS, 1994 <sup>45</sup>	Age ≤85 y, STEMI, ≤12 h§	250	Open label	APSAC 30 U over 2-5 min	No bolus, 15 IU/kg per hr† for 4 d; target aPTT 50-90 s	No heparin	325 mg/d	Death, recurrent MI, recurrent ischemia, angiographic patency	14 d

APSAC indicates anisoylated plasminogen-streptokinase activator complex (anistreplase); aPTT, activated partial thromboplastin time; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MU, mega units; SK, streptokinase; and tPA, tissue plasminogen activator (alteplase).

\*No dose adjustment unless otherwise specified. †Started after 12 h in ISIS-2 Pilot and after 4 hours in DUCCS.

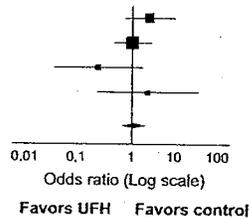
‡The initial aspirin dose was 300 mg PO in UK centers and 200 mg IV in continental European centers.

§Stratified by time to presentation: 0 to 6 h or 6 to 12 h. (from: *Circulation* 2005;112: 3855-67)<sup>23</sup>

Neither the individual randomized trials nor their pooled results showed a significant reduction in death or reinfarction with UFH compared with no heparin or placebo. As seen in Figure 17, iv UFH during hospitalization did not reduce reinfarction (3.5% vs 3.3%; OR, 1.08; 95% CI 0.58 to 1.99) or death (4.8% vs 4.6%; OR, 1.04; 95% CI 0.62 to 1.78), and, as shown in Table 14, did not increase major bleeding (4.2% vs 3.4%; OR, 1.21; 95% CI 0.67 - 2.18) but increased minor bleeding (19.6% vs 12.5%; OR, 1.72; 95% CI 1.22 - 2.43).

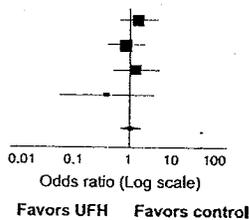
**Reinfarction During Hospitalization\***

Study	UFH	Control	OR	95% CI
DUCCS, 1994	9/128	4/122	2.23	0.70 - 7.44
ECSG, 1992	10/324	10/320	0.99	0.40 - 2.40
ISIS-2 Pilot, 1987	1/106	5/103	0.19	0.02 - 1.63
OSIRIS, 1992	2/64	1/64	2.03	0.18 - 22.99
<b>Total</b>	<b>22/622</b>	<b>20/609</b>	<b>1.08</b>	<b>0.58 - 1.99</b>



**Death During Hospitalization**

Study	UFH	Control	OR	95% CI
DUCCS, 1994	12/128	8/122	1.47	0.58 - 3.74
ECSG, 1992	9/324	11/320	0.80	0.58 - 1.96
ISIS-2 Pilot, 1987	8/106	6/103	1.32	0.44 - 3.95
OSIRIS, 1992	1/64	3/64	0.32	0.03 - 3.19
<b>Total</b>	<b>30/622</b>	<b>28/609</b>	<b>1.04</b>	<b>0.62 - 1.78</b>



**Figure 17 UHF vs control: reinfarction and death.**

(From: *Circulation* 2005; 112: 3855-67)<sup>23</sup>

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

The above results provide no evidence for a benefit of iv UFH for preventing reinfarction or death in patients with STEMI who are routinely treated with aspirin and thrombolysis. However, the UFH trials were underpowered because they included a total of only 1239 randomized patients with 42 re-infarctions and 58 deaths. This small number of events is reflected by the wide CIs for the estimates of treatment effect, which do not exclude moderate and plausible benefits or increases of 30% to 40% in reinfarction or death.

Collins et al performed a meta-analysis of 26 randomized trials involving 73,000 patients<sup>10,48</sup> who received either UFH by any route (sc or iv) or no heparin as an adjunct to thrombolytic therapy in patients with acute STEMI. The majority of patients included in this meta-analysis received UFH by the sc route<sup>6,9</sup>, and 21 of the 26 included trials did not use routine aspirin therapy.

An analysis restricted to trials that used aspirin revealed that UFH compared with no UFH significantly reduced the risk of death (8.6% vs 9.1%;  $P=0.03$ ) and reinfarction (3.0% vs 3.3%;  $P=0.04$ )<sup>10</sup>. However, major bleeding was also significantly increased (1.0% vs 0.7%;  $P<0.001$ ), and these investigators concluded that routine administration of either iv or sc UFH as an adjunct to thrombolytic therapy in patients with acute STEMI was not warranted, irrespective of which thrombolytic agent was used.

Other analyses restricted to patients who received iv UFH demonstrated no clear benefit of iv UFH<sup>49,50</sup>. No large-scale trials of iv UFH have been conducted in patients with STEMI, and it seems very unlikely that they will be performed in the future given the emergence of LMWH (see below).

Most randomized trials comparing different thrombolytic agents for the treatment of STEMI were performed with iv UFH, and newer fibrin-specific agents were approved on this basis. There is also evidence of improved infarct-related coronary artery patency when iv UFH is added to fibrin-specific thrombolytic agents<sup>51,52,53</sup>. However, in 2 of these trials, patients treated with iv UFH did not receive aspirin,<sup>51,52</sup> whereas in the third study<sup>53</sup>, in which all patients received aspirin, there was only a modest impact of iv UFH on patency.

Trials of other antithrombotic agents (e.g., glycoprotein IIb/IIIa inhibitors) suggest that improved patency does not necessarily translate into improved clinical outcomes<sup>54,55</sup>. In the absence of evidence of efficacy, concerns regarding safety assume greater importance. In the case of iv UFH, there is a consistent pattern of increased risk of bleeding for both major and intracranial bleeding and a significant increase in minor bleeding.

In conclusion, among aspirin-treated patients with STEMI who receive thrombolytic therapy, randomized trials comparing iv UFH with control have been underpowered and have not shown a benefit of UFH for preventing reinfarction or death. Despite this lack of evidence of efficacy of UFH for preventing reinfarction or death, iv UFH remains widely used in patients with STEMI, particularly in Western countries in which fibrin-specific thrombolytic agents are widely used. This practice follows current ACC/AHA guidelines<sup>1</sup> and European Society of Cardiology (ESC) guidelines<sup>47</sup> for the management of STEMI, which recommend iv UFH for patients treated with alteplase or other thrombolytic agents<sup>47</sup>.

### (2) *The potential advantages of LMWHs*

LMWH preparations are formed by controlled enzymatic or chemical depolymerization

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

producing saccharide chains of varying lengths but with a mean molecular weight of  $\approx 5000$ . Much of the potential advantages of the LMWHs centers around their enhanced ratio of anti-Xa : anti-IIa activity. The explanation for this is that a chain length of  $\geq 18$  saccharides is required to form a ternary complex between heparin, antithrombin, and thrombin. A critical pentasaccharide sequence is required for attachment of a heparin fragment to antithrombin, and an additional 13 saccharide residues are necessary to allow the heparin fragment to simultaneously attach itself to the heparin-binding domain of thrombin, thus creating the ternary complex. LMWH fragments of  $\leq 18$  saccharides retain the critical pentasaccharide sequence, which is all that is required for formation of a Xa:antithrombin: heparin complex.

This enhanced anti-Xa:IIa ratio offered by the LMWHs provides a therapeutic benefit. Because factor Xa generation occurs several steps earlier in the coagulation cascade than thrombin generation, inhibition of Xa has a profound effect on the later steps in coagulation, i.e., quenching a small amount of Xa may prevent the formation of much larger quantities of thrombin.

Other features of LMWHs that are of particular clinical relevance are a decreased sensitivity to platelet factor 4 and a more predictable anticoagulant effect along with lower rates of thrombocytopenia and HITS. In addition, the LMWHs are clinically attractive because of better bioavailability, a more consistent pattern of clearance, and ease of administration via the subcutaneous route. In theory, they allow clinicians to prescribe relatively unsupervised long-term self-administration of anti-thrombotic therapy by patients at home (i.e., "an insulin-like injection for coronary artery disease").

In addition, each LMWH has a unique profile for release of TFPI (tissue factor pathway inhibitor, which is a 276 amino-acid protease inhibitor), and, because LMWH have higher bioavailability, are able to release TFPI more efficiently than UFH.

Also, enoxaparin has been shown to be more efficient than UFH in binding to the heparin-binding domain of von Willebrand factor, which is known to be a risk factor for the development of coronary heart disease<sup>56</sup>.

### ***(3) Does LMWH provide a benefit (prevention of death or reinfarction) over placebo in patients with STEMI (who are routinely treated with aspirin and thrombolysis)?***

A recent meta-analysis of randomized trials in patients with STEMI revealed 4 trials of LMWH vs placebo<sup>23</sup>. Table 47 summarizes the study designs. Three trials used streptokinase<sup>57,58,59</sup>, and the fourth used either streptokinase or urokinase for thrombolytic therapy<sup>60</sup>. The initial dose of aspirin was between 100 and 325 mg followed by a maintenance dose of between 75 and 325 mg/d in the three trials in which this information was reported<sup>57,58,59</sup>, and the duration of LMWH was between 1 and 11 days. Two trials evaluated dalteparin<sup>57,58</sup>, one evaluated enoxaparin<sup>59</sup>, and 1 one evaluated reviparin<sup>60</sup>. All four studies were double-blind and placebo controlled, and follow-up was  $>99\%$  in the three studies for which these data were reported<sup>57,59,60</sup>.

**Table 47 LMWH vs Placebo: Trial Design**

Study	Eligibility	N	Blinding	Thrombolysis	Randomized Treatment			Primary Outcome	Follow-up
					LMWH	Control	Aspirin		
FRAMI, 1997 <sup>46</sup>	Q wave or STEMI	776	Double-blind	SK 1.5 MU over 1 h	Dalteparin 150 mg/kg BID for 7-11 d	Placebo	300 mg; then 160 mg/d	Echocardiographic LV thrombus, arterial embolism	3 m*
BIOMACS II, 1999 <sup>47</sup>	Age ≤80 y, STEMI or new LBBB	101	Double-blind	SK 1.5 MU over 1 h	Dalteparin 100 mg/kg, 2 doses	Placebo	300 mg; then 75 mg/d	Angiographic TIMI flow in infarct-related vessel	14-21 d
AMI-SK, 2002 <sup>48</sup>	Age >18 y, STEMI	496	Double-blind	SK 1.5 MU over 1 h	Enoxaparin 30 mg IV bolus, 1 mg/kg for 3-8 d†	Placebo	100-325 mg/d	Angiographic TIMI flow in infarct-related vessel	30 d
CREATE, 2005 <sup>11</sup>	STEMI or new LBBB, ≤12 h	15 570	Double-blind	SK or UK‡	Reviparin 3436-6871 IU BID for 7 d (weight adjusted)	Placebo	Dose not specified§	Death, MI, or stroke; death, MI, stroke, or recurrent ischemia	30 d

LV indicates left ventricular; MI, myocardial infarction; MU, mega units; SK, streptokinase; TIMI, Thrombolysis in Myocardial Infarction; and UK, urokinase. \*Only in-hospital outcomes are reported in the article. †Maximum of 100 mg for the first 2 doses. ‡27% did not receive thrombolysis. §97% received aspirin; 55% received clopidogrel or ticlopidine. (from: *Circulation* 2005;112: 3855-67)<sup>23</sup>

**Reinfarction, Stroke, Death:** There was a significant reduction of approximately one quarter in reinfarction (134 events [1.6%] vs 184 events [2.2%]; OR, 0.72; 95% CI, 0.58 to 0.90; number needed to treat [NNT]=167) and a 10% reduction in death (659 events [7.8%] vs 730 events [8.7%]; OR, 0.90; 95% CI, 0.80 to 0.99; NNT=111) during hospitalization/at day 7 among patients treated with LMWH compared with placebo (Table 48).

**Table 48 Reinfarction, stroke, and death during hospitalization/at 7 days in randomized heparin trials**

Outcome	Total N	UFH, n/N (%)	Control, n/N (%)	OR (95% CI)*
Reinfarction	1231	22/622 (3.5)	20/609 (3.3)	1.08 (0.58-1.99)
Death	1231	30/622 (4.8)	28/609 (4.6)	1.04 (0.62-1.78)
Stroke	1231	11/622 (1.8)	4/609 (0.7)	2.55 (0.85-7.68)
Intracranial bleeding	1231	5/622 (0.8)	1/609 (0.2)	2.30 (0.59-8.95)
Outcome	Total N	LMWH, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Reinfarction	16842	134/8421 (1.6)	184/8421 (2.2)	0.72 (0.58-0.90)
Death	16842	659/8421 (7.8)	730/8421 (8.7)	0.90 (0.80-0.99)
Stroke	16842	68/8421 (0.8)	57/8421 (0.7)	1.19 (0.84-1.70)
Intracranial bleeding	16842	23/8421 (0.3)	10/8421 (0.1)	2.18 (1.07-4.52)
Outcome	Total N	LMWH, n/N (%)	UFH, n/N (%)	OR (95% CI)
Reinfarction	7093	108/3588 (3.0)	181/3505 (5.2)	0.57 (0.45-0.73)
Death	7093	172/3588 (4.8)	185/3505 (5.3)	0.92 (0.74-1.13)
Stroke	7093	66/3591 (1.8)	47/3502 (1.3)	1.38 (0.95-2.01)
Intracranial bleeding	6851	39/3431 (1.1)	33/3420 (1.0)	1.18 (0.74-1.87)

\* No significant heterogeneity for any outcome; (from: *Circulation* 2005;112: 3855-67)<sup>23</sup>

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

This benefit remained evident at day 30 for both reinfarction (168 events [2.1%] vs 219 events [2.7%]; OR, 0.76; 95% CI, 0.62 to 0.93; NNT=167) and death (787 events [9.7%] vs 900 events [11.1]; OR, 0.86; 95% CI, 0.78 to 0.95; NNT=71) (Table 49).

**Table 49 Reinfarction, stroke and death during hospitalization/at 30 days in randomized heparin trials**

Outcome	Total N	LMWH, n/N (%)	Placebo, n/N (%)	OR (95% CI)*
Reinfarction	16167	168/8087 (2.1%)	219/8080 (2.7%)	0.76 (0.62–0.93)†
Death	16167	787/8087 (9.7%)	900/8080 (11.1%)	0.86 (0.78–0.95)
Stroke	16167	80/8087 (1.0%)	67/8080 (0.8%)	1.19 (0.86–1.65)
Outcome	Total N	LMWH, n/N (%)	UFH, n/N (%)	OR (95% CI)*
Reinfarction	5454	103/2770 (3.7%)	150/2684 (5.6%)	0.64 (0.50–0.84)
Death	7093	201/3588 (5.6%)	211/3505 (6.0%)	0.94 (0.77–1.14)
Stroke	5154	50/2624 (1.9%)	41/2530 (1.6%)	1.19 (0.79–1.81)

\*Unless indicated otherwise, there was no significant heterogeneity for any outcome. †P for heterogeneity 0.02. (from: *Circulation* 2005;112: 3855-67)<sup>23</sup>

There was significant heterogeneity for the pooled estimate for reinfarction at day 30, which can be attributed to the large and unexpected almost 4-fold excess of reinfarction in the BIOMACS II study among patients treated with LMWH compared with placebo.<sup>47</sup> However, this was a small study (n=101) with only a small number of re-infarctions (n=10), which were not significantly increased (OR, 3.91; 95% CI, 0.79 to 19.44).

There was a nonsignificant excess of strokes during hospitalization/at day 7 in patients treated with LMWH compared with placebo (68 events [0.8%] vs 57 events [0.7%]; OR, 1.19, 95% CI, 0.84 to 1.70). This was almost entirely accounted for by an increase in intracranial hemorrhage among patients treated with LMWH (23 events [0.3%] vs 10 events [0.1%]; OR, 2.18, 95% CI, 1.07 to 4.52; number needed to harm [NNH]=500). The increase in strokes with LMWH was also evident at 30 days (80 events [1.0%] vs 67 events [0.8%]; OR, 1.19; 95% CI, 0.86 to 1.65), but the absolute difference remained the same (a difference of 13 events at both time points).

**Bleeding** (Table 50): Among the 1272 patients for whom the data were available, there was a significant excess of minor bleeding during hospitalization/at day 7 among those treated with LMWH compared with placebo (97 events [15.1%] vs 33 events [5.2%]; OR, 3.24; 95% CI, 2.12 to 4.91). This analysis included only 2 studies, and there was statistically significant heterogeneity between them (P=0.003).

There also was a significant excess of major bleeds during hospitalization/at day 7 among 16 842 patients treated with LMWH compared with placebo (94 events [1.1%] vs 35 events [0.4%]; OR, 2.70; 95% CI, 1.83 to 3.99; NNH=143).

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)**Table 50 Bleeding during hospitalization/at 7 days in Randomized Heparin Trials**

Bleeding Outcome	Total N	UFH, n/N (%)	Control, n/N (%)	OR (95% CI)*
Minor bleeding	1022	101/516 (19.6%)	63/506 (12.5%)	1.72 (1.22–2.43)
Major bleeding	1231	26/622 (4.2%)	21/609 (3.4%)	1.21 (0.67–2.18)
Bleeding Outcome	Total N	LMWH, n/N (%)	Placebo, n/N (%)	OR (95% CI)*
Minor bleeding†	1272	97/641 (15.1%)	33/631 (5.2%)	3.24 (2.12–4.91)‡
Major bleeding	16842	94/8421 (1.1%)	35/8421 (0.4%)	2.70 (1.83–3.99)
Bleeding Outcome	Total N	LMWH, n/N (%)	UFH, n/N (%)	OR (95% CI)*
Minor bleeding	6393	739/3242 (22.8%)	612/3151 (19.4%)	1.26 (1.12–1.43)
Major bleeding	7093	117/3591 (3.3%)	89/3502 (2.5%)	1.30 (0.98–1.72)

\*No statistical heterogeneity for any bleeding outcome unless indicated otherwise. †The CREATE study<sup>60</sup> did not report minor bleeding. ‡P for heterogeneity 0.003. (from: *Circulation* 2005;112: 3855-67)<sup>23</sup>

Thus, LMWH compared with placebo *reduced* reinfarction by  $\approx 25\%$  and death by  $\approx 10\%$ . Six re-infarctions and 9 deaths were prevented during hospitalization/at day 7 for every 1000 patients treated with LMWH, at the cost of 7 major bleeds, including 2 intracranial bleeds. By 30 days, 6 re-infarctions and 14 deaths were prevented for every 1000 patients treated. Stroke was not significantly increased, but the observed excess of strokes with LMWH was equivalent to an increase of 2 events for every 1000 treated. This indicates that the benefits outweigh the harm. These analyses are based on data from >16 000 patients with STEMI. There was no convincing evidence of heterogeneity among different LMWH preparations tested, but the number of trials was small, and most of the data were obtained from the 15000-patient CREATE study in which reviparin was used<sup>60</sup>.

**(4) Does LMWH provide a benefit (prevention of death or reinfarction) over iv UFH in patients with STEMI (who are routinely treated with aspirin and thrombolysis)?**

A meta-analysis of randomized trials in patients with STEMI<sup>23</sup> revealed 6 trials (n=7098) of LMWH vs UFH NOT including the ExTRACT-TIMI 25 study under review (Table 51). Three of these studies (Table 51) used tenecteplase<sup>15,61,62</sup> two used alteplase<sup>63,64</sup> and one used streptokinase<sup>65</sup>. One study<sup>65</sup> did not administer aspirin until day 4; the remaining studies for which this information was available administered  $\geq 150$  mg initially followed by a maintenance dose between 75 and 325 mg daily<sup>15,61,62,64</sup>. Five of the 6 studies evaluated enoxaparin<sup>15,61,62,63,65</sup>; the remaining study evaluated dalteparin<sup>64</sup>. The duration of LMWH or UFH treatment was between 48 hours and 8 days.

All six trials reported adequate concealment of the randomized treatment sequence; however, none of the studies were double-blind. In 5 studies, follow-up was at least 99% complete<sup>15,61,62,63,65</sup>; in the remaining study completeness of follow-up was not reported<sup>64</sup>.

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

**Table 51 LMWH vs UFH: Trial Design**

Study	Eligibility	N	Blinding	Thrombolysis	Randomized Treatment			Primary Outcome	Follow-up
					LMWH*	UFH†	Aspirin		
ASSENT 3, 2001 <sup>49</sup>	Age >18 y; STEMI or LBBB, ≤6 h	4078	Open label	TNK 30–50 mg (weight adjusted)	Enoxaparin 1 mg/kg BID, ≤7 d	60 IU/kg bolus, then 12 IU/kg per h for 48 h <sup>‡</sup>	150–325 mg/d	In-hospital MI or RI or 30-day death	30 d
HART II, 2001 <sup>50</sup>	Age ≥18 y; STEMI or new LBBB, ≤12 h	400	Open label	tPA weight adjusted over 90 min	Enoxaparin 1 mg/kg BID, ≥3 d	4000–5000 IU bolus, then 15 IU/kg per hour for ≥3 d	Not specified	Angiographic 90-min TIMI flow	5–7 d
Baird et al, 2002 <sup>51</sup>	STEMI	300	Open label	SK 1.5 MU or APSAC 30 IU or tPA 100 mg	Enoxaparin 40 mg TID, 4 d	5000 IU bolus, then 30 000 IU over 24 h for 4 d	75–300 mg/d after day 4†	MI, death, readmit for UA	90 d
ENTIRE-TIMI 23, 2002 <sup>52</sup>	Age 21–75 y; STEMI, ≤6 h	242	Open label	TNK 0.53 mg/kg	Enoxaparin 1 mg/kg BID, ≤8 d	60 IU/kg, then 12 IU/kg per h for ≥3 d	100–325 mg/d§	Angiographic 60-min TIMI flow	30 d
ASSENT Plus, 2003 <sup>53</sup>	Age ≥18 y; STEMI or new LBBB; ≤6 h	439	Open label	tPA ≤100 mg over 90 min	Dalteparin first dose 90 IU/kg, then 120 IU/kg BID, 4–7 d	4000–5000 IU bolus, then 800–1000 IU/h for 48 h	150–325 mg/d	Angiographic TIMI flow	30 d
ASSENT 3 Plus, 2003 <sup>54</sup>	Age ≥18 y; STEMI or new LBBB, ≤6 h	1639	Open label	TNK 30–50 mg (weight adjusted)	Enoxaparin 1 mg/kg BID, ≤7 d	60 IU/kg, then 12 IU/kg per h for ≥3 d	100–325 mg/d¶	In-hospital MI or RI or 30-day death	30 d

APSAC indicates anisoylated plasminogen-streptokinase activator complex (anistreplase); LV, left ventricular; MI, myocardial infarction; MU, mega units; RI, refractory ischemia; TIMI, Thrombolysis in Myocardial Infarction; SK, streptokinase; TNK, tenecteplase; tPA, tissue plasminogen activator (alteplase); and UA, unstable angina. \*All enoxaparin trials administered initial iv bolus of 30–40 mg. Initial iv bolus of dalteparin was 30 IU/kg. †In each trial UFH was weight adjusted according to the results of the activated partial thromboplastin time. ‡No aspirin during the first 4 days. §Initial dose ≥160 mg PO or 250–500 mg IV. ¶Initial dose 150–325 mg/d. (from: *Circulation* 2005;112: 3855–67)<sup>23</sup>

**Reinfarction, Stroke, Death:** There was a significant reduction of ≈45% in reinfarction (108 events [3.0%] vs 181 events [5.2%]; OR, 0.57; 95% CI, 0.45 to 0.73; NNT=45) and a nonsignificant 8% reduction in death (172 events [4.8%] vs 185 events [5.3%]; OR, 0.92; 95% CI, 0.74 to 1.13) during hospitalization/at day 7 among patients treated with LMWH compared with UFH (Table 48). There was also a nonsignificant excess of strokes during hospitalization/at day 7 in patients treated with LMWH compared with UFH (66 events [1.8%] vs 47 events [1.3%]; OR, 1.38; 95% CI, 0.95 to 2.01). This was accompanied by a nonsignificant increase in intracranial hemorrhage among patients treated with LMWH (39 events [1.1%] vs 33 events [1.0%]; OR, 1.18; 95% CI, 0.74 to 1.87).

A similar pattern was evident at day 30 for both reinfarction (103 events [3.7%] vs 150 events [5.6%]; OR, 0.64; 95% CI, 0.50 to 0.84; NNT=53) and death (201 events [5.6%] vs 211 events [6.0%]; OR, 0.94; 95% CI, 0.77 to 1.14) (Table 49). The nonsignificant increase in strokes at 30 days remained evident (50 events [1.9%] vs 41 events [1.6%]; OR, 1.19; 95% CI, 0.79 to 1.81), but there were fewer events reported than at the earlier time point because 30-day stroke data were not available from 2 studies<sup>62,65</sup>.

One factor that may contribute to the difference in effectiveness of LMWH compared with UFH to prevent re-infarction in patients with STEMI is the differences in the duration of anticoagulation. In direct head-to-head comparisons, most patients receiving UFH were treated for 2 to 4 days, whereas those receiving LMWH were mostly treated for between 4 and 8 days. Meanwhile, the longer half-life of LMWH compared with UFH may have blunted or eliminated the rebound procoagulant effect that occurs after intravenous UFH is stopped<sup>56,66</sup>. These data underscore the importance of an adequate duration of LMWH

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

therapy when used as adjunctive therapy to thrombolysis in patients with STEMI.

The role of LMWH in the context of new and emerging antithrombin therapies for patients with STEMI still needs to be studied. None of the LMWH trials in the meta-analysis was performed in patients treated with *combined clopidogrel and aspirin therapy*. In the CLARITY-TIMI 28 trial<sup>21</sup> in which clopidogrel vs placebo was administered to STEMI patients in addition to aspirin, patients treated with LMWH plus clopidogrel plus aspirin, in addition to a standard fibrinolytic therapy, had a high rate of infarct-related artery patency (90.9%), and low rates of CV death (3.2%), recurrent MI (30.%) and major bleeding (1.8%). There have been no phase 3 trials directly comparing LMWH with direct thrombin inhibitors in patients with STEMI, but, unlike LMWH in the ExTRACT-TIMI 25 and other trials, direct thrombin inhibitors have not been shown to reduce death<sup>67,68</sup>.

*Bleeding:* There was a significant increase in minor bleeding during hospitalization/at day 7 among patients treated with LMWH compared with UFH (739 events [22.8%] vs 612 events [19.4%]; OR, 1.26; 95% CI, 1.12 to 1.43) (Table 50). A similar pattern was evident for major bleeds, although the increase was not significant (117 events [3.3%] vs 89 events [2.5%]; OR, 1.30; 95% CI, 0.98 to 1.72). In 2 trials, intracranial hemorrhage was not included as part of major bleeding<sup>64,69</sup>.

Pooled data from randomized comparisons on >7000 patients with STEMI (with most of the data from 5 studies in which enoxaparin was used) indicate that LMWH compared with iv UFH reduced the risk of reinfarction by 43% with no reduction in death. Although there was no significant difference in the incidence of stroke between the 2 treatment groups, stroke was increased among those treated with LMWH. Thus, it appears that LMWH administered for 4 to 8 days compared with placebo reduces reinfarction by approximately one quarter and death by 10%, and when directly compared with UFH reduces reinfarction by almost one half. The benefits of LMWH are seen early and remain evident at 30 days. These data suggest that LMWH should be the preferred antithrombin in this setting.

### 8.7 Postmarketing Risk Management Plan

Not applicable.

### 8.8 Other Relevant Materials

Not applicable.

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

## 9. OVERALL ASSESSMENT

### 9.1 Conclusions

The ExTRACT-TIMI 25 study enrolled 20,506 patients with STEMI who were eligible for fibrinolytic therapy (at the treating physician's discretion, streptokinase [capped at 5000 patients], alteplase, tenecteplase or reteplase). The study was conducted during 24-Oct-2002 through 01-Oct-2005 at 674 sites in 48 countries including the United States (9 sites).

Patients were randomized using a central, computerized system via an interactive voice response system to receive either enoxaparin (for the duration of the index hospitalization or 8 days, whichever came first) or UFH (for 48 hours, the current standard of treatment). The double-blind study drugs were administered between 15 minutes before and up to 30 minutes after start of fibrinolytic therapy.

In the ExTRACT-TIMI 25 study, the doses of enoxaparin were:

- Patients with STEMI < 75 years old: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg sc *every 12 hours*;
- Patients with severe renal impairment: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg SC *once daily*;
- Geriatric patients ≥75 years of age: *0.75 mg/kg sc every 12 hours without an initial IV bolus.*

The mean duration for enoxaparin/enoxaparin placebo sc injection was 6.6 days with 74.5% treated for ≥6 days (median duration = 7 days). The mean duration of UFH/UFH placebo iv infusion was 53.7 hours with 89.6% of the total population treated for ≥36 hours (median duration = 2 days).

All patients received 150 to 325 mg of nonenteric-coated aspirin orally (chewed) or 500 mg iv as soon as they were identified with STEMI, and maintenance therapy with 75 to 325 mg aspirin once daily orally for a minimum of 30 days.

The primary efficacy endpoint was a composite of all-cause death and non-fatal myocardial re-infarction within 30 days after randomization. Patients were followed up for 30 days (visit in person or by telephone contact) for the primary and secondary efficacy and safety endpoints of the study. Six and 12-month follow-up visits were made by telephone contact.

The main secondary efficacy endpoint was the composite of death from any cause, non-fatal myocardial re-infarction, or recurrent myocardial ischemia leading to urgent revascularization in the first 30 days. An additional secondary endpoint (net clinical benefit) was the composite of death from any cause, non-fatal myocardial re-infarction, or non-fatal disabling stroke.

The tertiary efficacy endpoints were:

- (i) the incidence of severe congestive heart failure alone or in combination with all-cause

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

mortality and non-fatal myocardial re-infarction within 30 days after randomization, and

- (ii) the incidence of all-cause mortality, non-fatal myocardial re-infarction, non-fatal disabling stroke, and myocardial ischemia leading to urgent revascularization alone or in combinations at 48 hours and at 8 days after randomization.

Of 20,506 patients randomized (10,273 enoxaparin and 10,233 UFH), 27 (17 enoxaparin and 10 UFH) did not receive study drug and had no follow-up information. Thus, the ITT population was 20,479 (10,256 enoxaparin and 10,223 UFH) patients.

In brief, patients were comparable at baseline regarding demographic and cardiovascular characteristics. These patients had prolonged ( $\geq 20$  minutes) ischemic symptoms of rest  $\leq 6$  hours prior to randomization, the mean time ( $\pm$ SD) from symptom onset to randomization being  $3.26 \pm 7.29$  hours in the enoxaparin group, and  $3.17 \pm 1.39$  hours in the UFH group. Only 126 (1.2%) patients in enoxaparin group and 115 (1.1%) patients in UFH group were randomized  $> 6$  hours after symptom onset.

The qualifying infarction was treated with medical therapy alone in 74.3% of patients, with PCI in 23.0% (as rescue therapy in 2.8%, and as an urgent or elective procedure in 20.2%), and coronary artery bypass surgery in 2.8% of patients.

A fibrinolytic agent was administered to 99.7% patients, with 79.5% receiving a fibrin-specific agent and 20.2% (4139 patients) receiving streptokinase. Three patients in enoxaparin group and 1 in UFH group did not receive fibrinolytic therapy. Use of fibrinolytic agent was comparable between the enoxaparin and UFH groups, being treated with streptokinase in 20.2% and 20.1%, TNK-tPA (Tenecteplase) in 19.3% and 19.6%, Reteplase in 5.5% and 5.4%, and Alteplase in 55.0% and 54.8%, respectively, of patients. The median time from onset of symptoms to start of fibrinolytic therapy was 3.2 hours.

Concomitant medications prior to hospitalization were comparable between the enoxaparin and UFH groups, with aspirin in 94.8% and 95.4%,  $\beta$ -blockers (excluding eye drops) in 85.9% and 85.5%, ACE inhibitors in 78.5% and 77.8%, statins in 69.5% and 69.5%, clopidogrel in 27.2% and 28.7%, oral anticoagulants in 2.1% and 2.5%, and thrombolytics (other than those of index MI) in 4% and 0.5%, respectively, of patients.

There were also 6 previous studies conducted between 1995 and 2005, which enrolled an additional 10,171 patients with STEMI. Of these:

- ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23, and HART II were *open-label* studies, and
- AMI-SK and TETAMI studies were *double-blind, placebo-controlled* studies, of which
  - AMI-SK study evaluated reperfusion (TIMI flow grade 3) by angiography, and
  - TETAMI study enrolled *non-thrombolized* patients with STEMI (i.e., *STEMI patients ineligible for reperfusion*) only, and showed that enoxaparin did *not* reduce the 30-day incidence of death, reinfarction and recurrent angina significantly compared with UFH in non-reperfused STEMI patients.

A clinically important difference between the ExTRACT-TIMI 25 study and the 6 previous studies is that in the 6 previous studies, enoxaparin was administered without dose modifications for age or renal impairment.

Due to differences in study designs and endpoints, no integrated analyses were performed

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

on efficacy and safety data from the ExTRACT-TIMI 25 study with efficacy and safety data from the 6 previous studies.

### ***Efficacy conclusions:***

The ExTRACT-TIMI 25 trial showed that enoxaparin significantly ( $p = 0.000003$ ) reduced the incidence of the composite primary efficacy endpoint (all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group vs 12% in the UFH group, 17% relative risk reduction).

This benefit is contributed mainly by a significant reduction in the incidence of non-fatal myocardial re-infarction (3.0% in enoxaparin group vs 4.5% in UFH group, 33% relative risk reduction,  $p < 0.001$ ), whereas the reduction in all-cause death (6.9% in enoxaparin group vs 7.5% in UFH group, 8% relative risk reduction) was not statistically significant ( $p = 0.11$ ).

The time-to-composite-endpoint (of death or non-fatal myocardial re-infarction) also showed a statistically significant reduction in the enoxaparin group compared to the UFH treatment group (HR = 0.83, 95% CI 0.77 – 0.90,  $P < 0.001$ ).

The treatment benefit of enoxaparin became evident at 48 hours, and was significantly positive at Day 8 and at Day 30.

This clinical benefit of treatment with enoxaparin was consistently demonstrated:

- across pre-specified subgroups of
  - age (<75 years vs  $\geq 75$  years),
  - infarct location,
  - presence of prior MI,
  - presence of diabetes mellitus,
  - presence of severe renal function impairment,
  - treatment with PCI or medical treatment,
  - type of fibrinolytic agent used,
  - concomitant medications with the exception of non-use of  $\beta$ -blockers, and
  - severe heart failure or cardiogenic shock (Killip Class III/IV),
- as positive findings when either myocardial ischemia leading to urgent revascularization or disabling stroke were added to the primary efficacy endpoint (first and main secondary efficacy and other secondary efficacy endpoints), and
- as positive findings in the tertiary composite endpoints.

This clinical benefit produced by enoxaparin appears to be limited to 30 days post-randomization. In the ExTRACT-TIMI 25 study, the Kaplan-Meier curves for death up to 12 months post-randomization for enoxaparin and UFH run closely together. This observation was also found in the long-term results of the ASSENT 3 study.

Despite the separation of the survival curves favoring enoxaparin over the follow up period of 12 months for composite endpoints of:

- (a) death and myocardial re-infarction, and
- (b) death, myocardial re-infarction and disabling stroke,

an analysis of clinical events at 6- and 12- months showed an excess of deaths and

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

myocardial re-infarction in the enoxaparin treatment group when

- (1) deaths at day 30 post-randomization were excluded, and
- (2) patients who experienced the composite primary efficacy endpoint (death or non-fatal myocardial re-infarction) were excluded.

***Safety conclusions:***

The ExTRACT-TIMI 25 study provided safety data for 20,327 patients with STEMI (enoxaparin: 10,176 patients; UFH: 10,151 patients) who received at least one dose of study treatment.

The primary safety endpoint was TIMI major hemorrhage within 30 days after randomization. The Fisher's Exact test was used to evaluate differences between the two treatment groups for this primary safety endpoint.

The majority (82%) of patients in each group completed the assigned treatment regimen. 17.6% (1790 of 10,256) patients in enoxaparin group and 18% (1830 of 10,223) patients in UFH group discontinued, most frequently due to a hemorrhagic AE (34.1% in enoxaparin group vs 24% in UFH group) or PCI-related reasons (48.5% (128 of 525) patients in enoxaparin group and 51.5% (136 of 625) patients in UFH group).

The sponsor also provided safety data for 10,040 randomized patients with STEMI (4128 enoxaparin patients, 5673 UFH patients, and 239 placebo patients) from 6 previously conducted studies. A majority (58%) of patients in each of the 6 studies completed the assigned treatment. Hemorrhagic events were the most frequent AEs that resulted in treatment discontinuation in all of the 6 previous studies.

The safety findings in the ExTRACT-TIMI 25 study were as follows:

1. Enoxaparin was associated with an *increase* in adjudicated TIMI major bleeding compared with UFH in patients with STEMI (2.1% vs 1.4%,  $p < 0.0001$ ).
2. No statistically significant difference ( $p = 0.1443$ ) was detected in ICH between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).
3. The frequencies of non-hemorrhagic AEs were similar between treatment groups.
4. The results of subgroup analyses for the primary safety endpoint in the ExTRACT study did not identify treatment-by-subgroup interactions.

***Efficacy vs safety:***

When the balance of efficacy and safety as "net-clinical-benefit" was assessed using 3 composite endpoints bf:

- death/re-infarction/nonfatal disabling stroke,
- death/re-infarction/ nonfatal major bleeding, and
- death/re-infarction/non-fatal ICH,

the incidence of events for each of the composite endpoints was significantly ( $P < 0.001$  for all comparisons) lower at 30 days in the enoxaparin group compared with the UFH group. Reductions in the absolute event rates of 1.8 to 2.2 percentage points corresponded to relative risk reductions ranging from 14% to 18%, supporting the overall positive beneficial effect of enoxaparin on both efficacy and clinically important safety endpoints.

## 9.2 Recommendation on Regulatory Action

From an efficacy perspective, the ExTRACT-TIMI 25 study showed that enoxaparin significantly ( $p = 0.000003$ ) *reduced* the incidence of the composite primary efficacy endpoint (all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group vs 12% in the UFH group, 17% relative risk reduction).

From the safety perspective, enoxaparin was associated with an *increase* in adjudicated TIMI major bleeding at 30 days compared with UFH in patients with acute STEMI (2.1% vs 1.4%,  $p < 0.0001$ ), without a statistically significant ( $p = 0.1443$ ) increase in intracranial hemorrhage (ICH) between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).

The net clinical benefit favored enoxaparin-treated patients: for every 1000 STEMI patients treated with enoxaparin, there would be:

- 6 fewer deaths,
- 15 fewer non-fatal myocardial re-infarctions, and
- 7 fewer episodes of urgent revascularization,

at a cost of an increase of 4 non-fatal major hemorrhages, with no increase in the number of non-fatal intracranial hemorrhage.

Based on the finding of a net clinically important beneficial effect of enoxaparin in the balance of efficacy and safety endpoint events in STEMI patients treated with enoxaparin in the ExTRACT-TIMI 25 study, I recommend “**approval**” for this application after the sponsor has complied with the changes I suggested in the “Indications” and “Clinical Studies” sub-sections of “Section 9.4 Labeling Review” of this clinical review.

## 9.3 Recommendation on Postmarketing Actions

Not applicable.

### 9.3.1 Risk Management Activity

Not applicable.

### 9.3.2 Required Phase 4 Commitments

Not applicable.

### 9.3.3 Other Phase 4 Requests

Not applicable.

### 9.4 Labeling Review

The sponsor's proposed "Indication" for this NDA is as follows:

**1.4 Lovenox Injection is indicated for the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).**

My suggested changes and rationale are as follows:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

**Rationale:** In the ExTRACT-TIMI 25 trial in support of this application, all 20,506 patients except 3 patients in enoxaparin group and 1 patient in UFH group did not receive fibrinolytic therapy. The clinical benefit produced by enoxaparin appears to be limited to 30 days post-randomization in the ExTRACT-TIMI 25 trial (Please see Section 9.1 Efficacy conclusions).

The TETAMI trial, which enrolled 1224 STEMI patients who were not eligible for thrombolytic therapy or primary PTCA/stent placement, showed that enoxaparin did *not* significantly reduce the 30-day incidence of death, non-fatal myocardial re-infarction or recurrent angina compared with UFH in these non-reperfused STEMI patients.

### 9.5 Comments to Applicant

Not applicable.

## 10. APPENDICES

### 10.1 Review of Individual Study Reports

#### 10.1.1 Review of ExTRACT-TIMI 25 study

##### ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis In Myocardial Infarction Study 25)

*A randomized, double-blind, double-dummy, parallel group, multinational, clinical study to evaluate the efficacy and safety of enoxaparin versus unfractionated heparin in patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy.*

#### *Summary*

ExTRACT-TIMI 25 is a randomized, double-blind, double-dummy, parallel group, multinational, clinical trial designed to provide definitive data on the efficacy and safety of a strategy of enoxaparin throughout index hospitalization vs standard treatment with UFH as adjunctive antithrombin therapy in patients with STEMI who are eligible for fibrinolysis.

#### *Objectives*

The primary objective was to determine if enoxaparin, when compared with UFH, would reduce the composite endpoint of all-cause mortality and non-fatal myocardial infarction within 30 days after randomization in patients with STEMI who receive fibrinolytic therapy.

The secondary objective was to determine if enoxaparin, when compared with UFH, would reduce the following composite endpoints: (a) all-cause mortality, non-fatal reinfarction, and myocardial ischemia leading to urgent revascularization and (b) all-cause mortality, non-fatal myocardial reinfarction, and non-fatal disabling stroke.

The tertiary objective was to determine if enoxaparin, when compared with UFH, would reduce the following: (a) the incidence of severe congestive heart failure alone or in combination with all-cause mortality and non-fatal myocardial infarction within 30 days after randomization and (b) the incidence of all-cause mortality, non-fatal myocardial infarction, nonfatal disabling stroke, and myocardial ischemia leading to urgent revascularization alone or in combinations at 48 hours and at 8 days after randomization.

#### *Study design*

ExTRACT-TIMI 25 is a randomized, double-blind, double-dummy, parallel group, multinational, clinical trial with an active control (UFH). A network of 850 sites in 47 countries was planned for the trial. Enrollment commenced in October 2002 with a projected sample size of approximately 21000 patients. During 24-Oct-2002 through 01-Oct-2005, 20506 patients underwent randomization at 674 sites in 48 countries (9 sites in the U.S.).

Patients with STEMI who are eligible to receive fibrinolytic therapy are included in the study. The enrollment criteria were similar to other large phase 3 trials of fibrinolysis for STEMI and were designed to exclude patients with cardiovascular or hematologic conditions that place them at an unacceptable risk of serious bleeding if a fibrinolytic were administered (Table 52).

## Clinical Review

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

**Table 52 Major enrollment criteria for ExTRACT-TIMI 25**

### Inclusion criteria

Patients with STEMI meeting all of the following criteria will be eligible for enrollment:

1. Male or non-pregnant female  $\geq 18$  years
2. Prolonged ( $\geq 20$  min) ischemic symptoms at rest  $\leq 6$  h before randomization,
3. ST-segment elevation of 0.1 mV in 2 or more limb leads or 0.2 mV in 2 or more contiguous precordial leads or left bundle-branch block
4. Scheduled to undergo reperfusion therapy with streptokinase, tenecteplase, alteplase, or reteplase

### Exclusion criteria

#### *Cardiovascular*

1. Cardiogenic shock or acute pericarditis
2. Symptoms suggestive of aortic dissection
3. Myocardial infarction precipitated by obvious provoking factors such as arrhythmia or infection

#### *Hemorrhagic risk*

1. Minor head trauma or any other trauma occurring after the index acute myocardial infarction
2. Active or recent bleeding episode ( $< 3$  mo)
3. History of bleeding diathesis or platelet disorder
4. Any single reliable recording of systolic blood pressure  $> 180$  mm Hg and/or diastolic blood pressure  $> 110$  mm Hg before randomization
5. History of stroke, transient ischemic attack, or hemorrhagic cerebrovascular disease
6. Any head trauma within 6 mo
7. Major surgery within 3 mo before randomization
8. Traumatic or prolonged cardiopulmonary resuscitation ( $> 2$  min) within 2 wk before randomization

#### *Prior or concomitant pharmacological therapy*

1. Administration of abciximab, within the previous 7 d or eptifibatid or tirofiban within the previous 24 h before randomization
2. Current therapy with oral anticoagulants or an international normalized ratio of  $> 1.5$
3. Administration of a low-molecular-weight heparin within 8 h before randomization

#### *General*

1. Known renal insufficiency with serum creatinine  $> 220$   $\mu\text{mol/L}$  (2.5 mg/dL) for men and  $> 175$   $\mu\text{mol/L}$  (2.0 mg/dL) for women when assessed before baseline examination
2. Advanced neoplastic or other life-threatening disease with a life expectancy of  $< 12$  mo
3. Women of childbearing potential except if postmenopausal, surgically sterile, or using accepted method(s) of birth control or having a negative pregnancy test.

Patients with diminished renal clearance were excluded to minimize the potential for excessive accumulation of enoxaparin. Patients who had been treated with a low-molecular-weight heparin within 8 hours before screening for enrollment were also excluded because of uncertainty about the level of residual anti-Xa activity and difficulty in constructing a safe dosing regimen of either study drug.

Patients were to receive, at the treating physician's discretion, streptokinase, alteplase, tenecteplase, and reteplase according to the manufacturers' instructions for the treatment of STEMI. A cap of 5000 patients receiving streptokinase (commonly used in European countries) was planned to ensure the availability of adequate data on the 3 other fibrinolytics. The sponsor submitted that although no phase 2 trial data supporting the use of enoxaparin with reteplase exist, the rationale for including reteplase in the permitted list of fibrinolytics was based on (a) its similarity to tissue plasminogen activator (tPA) for which phase 2 data for its use in conjunction with enoxaparin exist and (b) the desire to provide a comprehensive assessment of enoxaparin vs UFH across all the fibrinolytics in common clinical use.

There was a 1:1 randomization ratio between patients allocated to enoxaparin and those allocated to UFH (Figure 18), with the use of a central, computerized system. Randomization was accomplished using an interactive voice response system, and the schedule was designed to provide a similar distribution of patients allocated to enoxaparin and to UFH across all 4 fibrinolytic drugs.

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NDA 22-138

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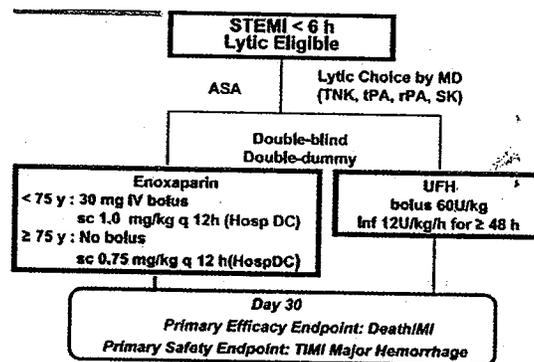


Figure 18 Schema for the ExTRACT-TIMI 25 trial.

Patients with STEMI presenting < 6 hours after the onset of symptoms and eligible to receive fibrinolytic therapy are randomized to receive enoxaparin or UFH in a double-blind, double dummy design. HospDC, hospital discharge; TNK, tenecteplase; tPA, tissue plasminogen activator; rPA, reteplase; SK, streptokinase.

### Study drug administration

Double-blind study medication was administered between 15 minutes before and up to 30 minutes after the start of fibrinolytic therapy. The dose, mode of administration, and treatment duration of the selected fibrinolytic must be in accordance with the approved label for the treatment of STEMI. The time between randomization and administration of the study drug should be as short as possible (within 30 minutes).

All patients received 150 to 325 mg of nonenteric-coated ASA orally (chewed) or 500 mg iv as soon as they are identified with STEMI unless they received at least 325 mg of ASA within the prior 24 hours or contra-indications to ASA are present. After the first 24 hours, maintenance therapy with 75 to 325 mg of ASA once daily orally (coated or uncoated) is administered for a minimum of 30 days. Alternative antiplatelet agents such as clopidogrel may be used at the investigator's discretion in patients with an allergy to ASA, or they could be added to aspirin at the investigator's discretion.

ExTRACT-TIMI 25 is designed to test 2 antithrombotic strategies: UFH administered for at least 48 hours (the current standard<sup>1</sup>) vs enoxaparin administered for the duration of the index hospitalization or 8 days, whichever comes first. Antithrombotic therapy throughout the index hospitalization is strictly via double-blind study medication. Specifically, the protocol specifies that open-label UFH or low-molecular-weight heparins should *not* be used unless the patient is referred for coronary artery bypass graft surgery, in which case the double-blind medication may be discontinued and replaced with an infusion of open-label UFH 6 hours before surgery at the discretion of the treating physician.

### Enoxaparin dosing regimen

Enoxaparin/matching placebo (drug A) (Figure 18) administration starts with a fixed 30 mg iv bolus injection for patients <75 years. Patients ≥ 75 years do not receive the 30 mg iv bolus.

Within 15 minutes after the intravenous bolus, patients who are < 75 years receive a sc injection with a dose of 1.0 mg/kg. Patients who are ≥ 75 years receive a sc injection of 0.75 mg/kg.

The same doses are injected sc every 12 h until hospital discharge or for a maximum of 8 days (whichever comes first). For the first 2 sc injections, a maximum dose of 100 mg (for those < 75 years) or 75 mg (≥ 75 years old) is administered even when the patient's body weight is >100 kg.

## Clinical Review

Khin Maung U

NDA 22-138

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To minimize the risk of bleeding, the iv bolus is omitted for patients who had received open-label UFH ( $\geq 4000$  U) < 3 hours before randomization and dosing adjustments are made for patients who are discovered to have or develop severe renal impairment (creatinine clearance  $\leq 30$  mL/min) after randomization.

The rationale for a lower dose in elderly patients ( $\geq 75$  years) is as follows. Enoxaparin is mainly eliminated by renal excretion, and elderly patients tend to have decreased renal clearance. Based on pharmacokinetic simulations with data from normal and renal function impaired patients, a 25% reduction in the maintenance dose of enoxaparin was selected to maintain similar anti-Xa levels for patients < 75 years and for those  $\geq 75$  years in the trial.

### *Unfractionated heparin dosing regimen*

Unfractionated heparin/matching placebo (drug B) administration is started with an intravenous bolus injection of 60 U/kg with a maximum of 4000 U. Within 15 minutes after the intravenous bolus, patients are started on an intravenous infusion of 12 U/kg per hour with a maximum of 1000 U/h. Adjustments to the infusion are performed according to the patient's activated partial thromboplastin time (aPTT). The intravenous infusion must be continued for at least 48 hours. Continuation of the infusion of UFH beyond 48 hours is at the treating physician's discretion. To minimize the risk of bleeding, the intravenous boluses of both blinded study drugs are omitted for patients who received open-label UFH ( $\geq 4000$  U) within 3 hours before randomization.

### *Patients requiring CABG surgery*

Both blinded drugs A and B should be discontinued  $\geq 6$  h (preferably 10 h) prior to the surgery, whenever possible. The treatment allocation should remain blinded, and the patient should continue with all further scheduled visits according to the protocol.

### *Antithrombotic therapy before PCI*

At screening, prior to randomization, if PCI is planned within the initial 48 h, the patient is NOT to be randomized.

The protocol recommends that after randomization, a non-emergent PCI should be deferred for  $\geq 48$  h following randomization. However, if a rescue PCI for failed fibrinolysis (or in response to an episode of recurrent myocardial ischemia or infarction) is deemed necessary, it may be performed at any time during the study. Up to Day 8, if a PCI (urgent or elective) is planned, every effort should be made to continue both study drugs A and B in a blinded manner until the end of the PCI.

### *Antithrombotic therapy during PCI*

During PCI, it may be necessary to add 1 to 2 additional boluses of drugs A and/or B depending on the following (Figure 19):

- A blinded dose of 0.3 mg/kg of enoxaparin/placebo is administered iv if the last sc dose was 8 to 12 hours earlier, whereas no additional enoxaparin/placebo is administered if the last sc dose was administered in the prior 8 hours.
- The blinded UFH/placebo is dosed according to the activated clotting time (ACT) values, using a target of 200 seconds for patients receiving a glycoprotein IIb/IIIa inhibitor and 250 seconds for those not receiving a glycoprotein IIb/IIIa inhibitor.

If a closure device is used, the sheath is removed at the end of the PCI. If no closure device is used, the sheath is removed  $\geq 6$  h after the last iv or sc dose of blinded study drug.

### *Antithrombotic therapy after PCI*

The blinded study drug is not restarted after uncomplicated PCI procedures. However, in

occasional instances of patients in whom antithrombotic therapy is considered clinically necessary, the study drug is restarted after groin hemostasis is achieved.

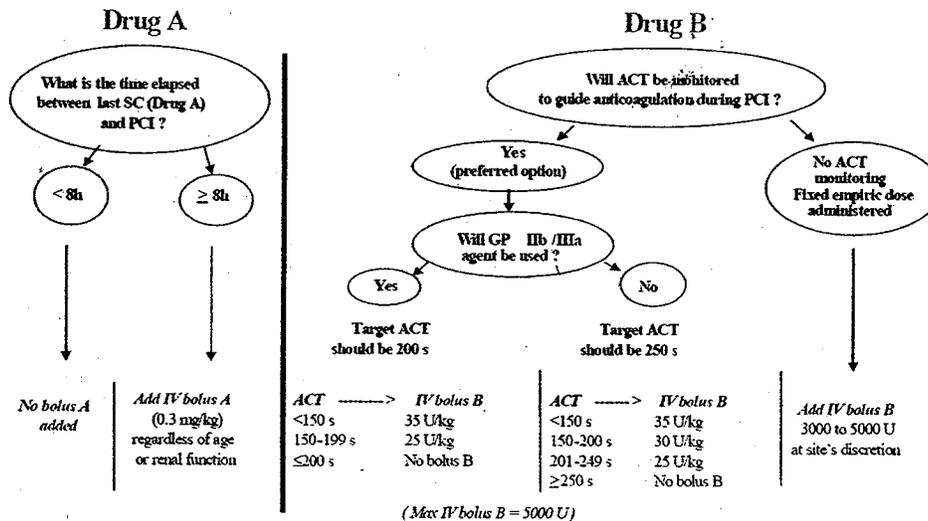


Figure 19 Administration of blinded study drug during PCI

Maintenance of double blind

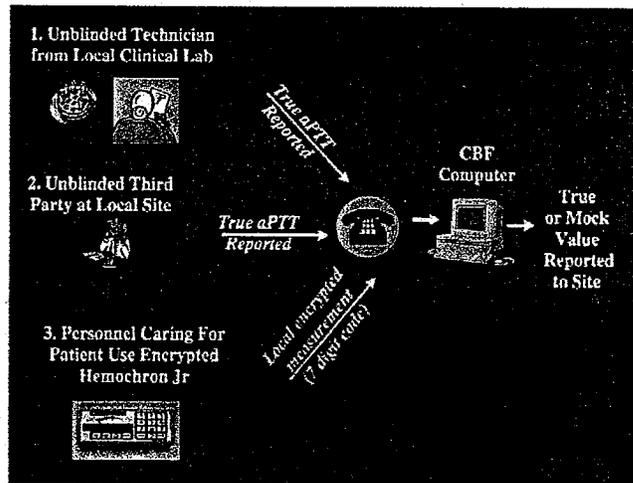


Figure 20 Options for maintaining double blind.

Investigators select from 1 of 3 options for maintaining the double blind during the trial:

- (1) an unblinded laboratory technician reports the true aPTT value via telephone to the central blinding facility (CBF);
- (2) an unblinded third party not involved in the patient's care at the clinical site receives the true aPTT measurement from an unblinded laboratory technician and reports it via telephone to the CBF; and
- (3) blinded personnel caring for the patient use a bedside encrypted device (Hemochron Jr; International Technodyne Corporation, Edison, NJ) to perform the aPTT analysis and receive a 7-digit code rather than the true aPTT result. The 7-digit code is reported by telephone to the CBF. The CBF, using the drug kit number for the specific patient, identifies whether the patient has been allocated to UFH or placebo for study drug B. For patients allocated to active UFH, the true aPTT is reported to the site; for patients allocated to placebo, a mock aPTT is reported to the site. The table of mock aPTT values is designed to mimic the anticipated number and type of adjustments to an infusion if UFH were truly being administered. Using any of the 3 methods, the personnel caring for the patient are informed only of the value reported back from the CBF and are unaware of whether it is a true or mock aPTT reading; thus, the double blind is maintained.

## Clinical Review

Khin Maung U

NDA 22-138

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As shown in Figure 20, to maintain the double blind, every patient receives both treatment regimens of which one is a matching placebo. Because UFH is monitored by aPTT (and ACT), the results of all aPTT (and ACT) measurements (excluding the baseline measurement) are made available only to a designated unblinded medical professional or in an encrypted fashion to personnel caring for the patient. True values are reported for patients assigned to active UFH whereas mock values are reported for patients assigned to enoxaparin via a central blinding facility.

### **Study procedures and follow-up**

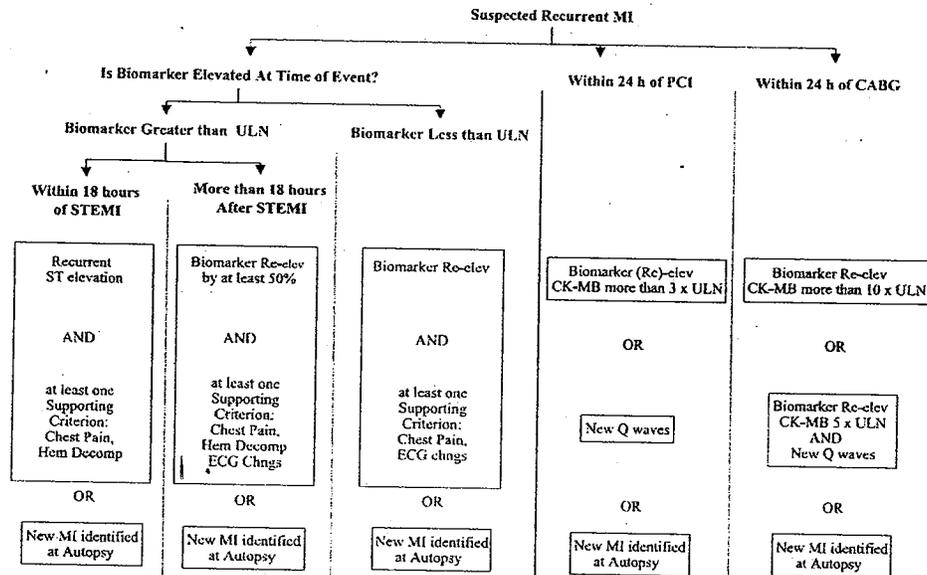
At 4 to 6 h after randomization, the aPTT is measured and only downward adjustment of the UFH/ placebo infusion is permitted. Within 12 hours of randomization, the patient's creatinine and actual weight are used to estimate creatinine clearance according to the Cockcroft-Gault formula and to adjust the dose of blinded enoxaparin/placebo. Elective PCI is discouraged within 48 hours of randomization because the focus of the trial is a comparison of 2 pharmacological strategies.

Patients were followed up for 30 days for the primary and secondary efficacy and safety components of the study. The 30-day follow-up visit is performed either in person or by telephone contact. All-cause mortality, myocardial reinfarction, and stroke at 6 and 12 months were also determined. The 6-month and 12-month follow-up visits are performed by telephone contact.

### **Study end point definitions**

**Death:** Death is defined as all-cause mortality.

**Recurrent myocardial infarction:** To meet the criteria for a myocardial reinfarction, the myocardial infarction must be a clinical event distinct from the index event. The criteria for reinfarction were adapted from the American College of Cardiology/ American Heart Association guidelines for management of patients with STEMI and are summarized in Figure 21.



**Figure 21 Algorithm for diagnosing recurrent MI after the index STEMI event.**

*CABG*, coronary artery bypass graft surgery; *Hem Decomp*, hemodynamic decompensation; *ECG chngs*, ECG changes; *ULN*, upper limit of normal. Modified from ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction<sup>1</sup>.

**Recurrent myocardial ischemia requiring urgent revascularization:** Recurrent ischemia requiring urgent revascularization is defined as any episode of recurrent myocardial discomfort or equivalent

## Clinical Review

Khin Maung U

NDA 22-138

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at rest for  $\geq 10$  minutes that prompts coronary revascularization (PCI or coronary artery bypass graft) during the same hospitalization. Documentation of ECG evidence of ischemia was not included in the definition of this endpoint to permit inclusion of events where the treating physician referred the patient for coronary revascularization on the basis of clinical symptoms, thus capturing events that incur a cost to the health care system in a comprehensive manner. Although the threshold for referral for coronary revascularization might vary across centers and countries, the double-blind nature of the trial would minimize bias in favor of one of the treatment arms.

**Recurrent severe myocardial ischemia:** Recurrent symptomatic myocardial ischemia is defined as ischemic-type discomfort at rest, lasting at least 10 minutes, and is associated with new, horizontal, or down-sloping ST-segment deviation.

**Severe congestive heart failure:** Severe congestive heart failure is defined as rales over  $>50\%$  of the lung fields that do not clear with coughing or evidence of pulmonary edema on chest radiograph.

**Cardiogenic shock:** Clinical criteria for cardiogenic shock are as follows:

Systolic blood pressure  $<90$  mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure  $\geq 90$  mm Hg **and**

- *either* End-organ hypoperfusion (cool extremities or urine output  $<30$  mL/h, and heart beat  $\geq 60$  beat/min)
- *or* The hemodynamic criteria are  $CI \leq 2.2$  L/min/M<sup>2</sup> body surface area *and* a pulmonary capillary wedge pressure of  $\geq 15$  mm Hg.

**Stroke:** A stroke is defined as the new onset of focal or global neurological deficit caused by ischemia or hemorrhage within or around the brain and lasting for  $>24$  hours.

**Bleeding events:** Bleeding is classified by the TIMI hemorrhage classification scheme (Table 53).

**Table 53 Criteria for TIMI hemorrhagic events**

	TIMI hemorrhage criteria*			
	ICH	Clinically overt (including imaging)	Hgb drop <sup>†,‡</sup> (g/dL)	Hct drop (%)
Major bleeding	x	x	$\geq 5$	$>15\%$
Minor bleeding	-	x	3 to $<5$	9% to $\leq 15\%$
Minimal bleeding	-	x	$<3$	$<9\%$

Hgb, hemoglobin; Hct = hematocrit; \*Accounting for the effect of transfusions on change in Hgb; ICH = intracranial hemorrhage; <sup>†</sup>One unit packed red blood cells = 1 g Hgb = 3% hematocrit.

<sup>‡</sup>Hemoglobin drop must be associated with clinically overt bleeding.

### **Adjudication of endpoint events by CEC**

A blinded, independent clinical events committee (CEC) adjudicates protocol-specific major clinical events such as cause of death, nonfatal myocardial infarction, the classification of stroke (e.g., hemorrhagic, ischemic), and major hemorrhagic events. Events for adjudication by the CEC are identified by 2 methods: (1) suspected events as noted by the local investigator on the case report form and (2) database-generated suspected events based on computer traps such as a drop in hemoglobin level  $\geq 5$  g/dL regardless of whether the event was identified by the investigator. The pertinent documents for each of the events are compiled by the data coordinating center and sent to the CEC members for review. Given the event-driven nature of the trial, the CEC meets on a regular basis (about once every 2 weeks) so that the operations committee has available a current estimate of the blinded aggregate number of events accumulated.

## Clinical Review

Khin Maung U

NDA 22-138

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### *Safety monitoring by DSMB*

An independent data safety monitoring board (DSMB) conducts ongoing safety monitoring periodically during the study. There will be 3 interim analyses occurring at 25%, 50%, and 75% of the total targeted primary endpoint events. Because UFH is routinely available and considered the standard antithrombin to support fibrinolytic therapy, at the first 2 interim analyses, consideration will be given to stopping the study if there is a strong mortality benefit (e.g.,  $P < 0.01$ ) favoring UFH. Additional factors considered by the DSMB at the first 2 interim analyses include major hemorrhage, stroke, recurrent nonfatal myocardial infarction, and other safety parameters. At the third interim analysis, consideration will be given to stopping the study if there are both (a) a strong mortality benefit ( $P < 0.01$ ) favoring enoxaparin and (b) the P value of the primary composite endpoint of all-cause mortality and nonfatal myocardial re-infarction has crossed the Lan-DeMets type of O'Brien Fleming stopping boundary.

### *Statistical considerations*

The sample size calculation is based on the assumption that the 30-day event rate for the composite primary endpoint in the UFH group will be 10.50% and that this will be reduced by 13.0% to 9.13% (i.e., relative risk reduction of 13% and absolute reduction of 1.37%) in the enoxaparin group. The predicted event rate in the UFH group and assumed benefit with the enoxaparin group are based on data from the ASSENT-3 study<sup>15</sup>. Based on the assumed event rate and treatment effect, to have approximately at least 90% power at the 5.0% significance level (2-sided), this event-driven trial is designed to enroll approximately 21,000 patients to accrue a total number of 2080 events.

A test for noninferiority of enoxaparin as compared with UFH is also planned. Noninferiority is defined as a relative risk of enoxaparin to UFH for the primary efficacy endpoint no larger than 1.03 to preserve 50% of the estimated treatment effect of UFH when added to aspirin. However, no sample size increase for this noninferiority hypothesis testing is planned.

All efficacy comparisons are to be analyzed according to the intention-to-treat principle. The analysis of the primary efficacy endpoint included all primary efficacy endpoints known to have occurred through 30 days after randomization and in the database that was locked on January 27, 2006. The sponsor also submits that they prospectively planned to summarize events occurring after day 30 that were identified on the visit at day 30 (range, day 31 to 38) in a 6-month study report.

The  $\chi^2$  test will be used for the comparison of treatment groups as a primary approach for the primary and secondary efficacy endpoints. However, to check for robustness of the study results, a time-to-event-based analysis will also be performed using a log rank test for the primary and secondary efficacy endpoints. The time of randomization will be used as the reference point. Hazard ratios and their 95% confidence intervals will also be provided for key comparisons.

The critical two-sided P value for the final analysis of the primary efficacy endpoint, after correction for interim analyses, was 0.043. A P value of less than 0.05 was the threshold for nominal significance for all other endpoints.

All safety analyses were performed according to the treatment actually received by the patient.

Subgroup analyses will be performed for the primary endpoint accounting for demographic as well as for important prognostic factors; however, the study has not been powered to detect treatment differences within these subgroups. Key subgroups include, but are not limited to, the following: age ( $\geq 75$  years vs  $< 75$  years), sex, race (white vs non-white), fibrinolytic drugs (streptokinase vs fibrin-specific thrombolytic drugs), and geographic region.

### *Monitoring of trial by operations committee*

An operations committee meets every 2 weeks to review the status of the trial, monitor for evidence of protocol violations at the site level, take corrective actions as needed, and track the aggregate

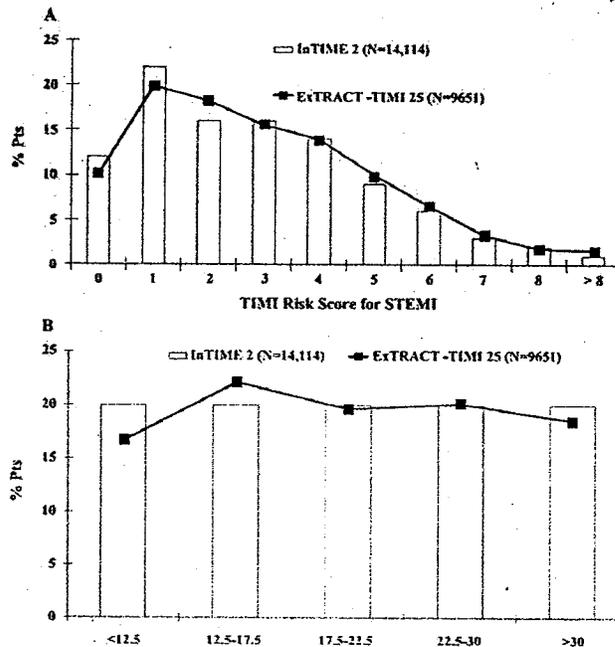
## Clinical Review

Khin Maung U

NDA 22-138

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number of primary endpoint events in a blinded fashion to estimate the timing of interim analyses and projected completion of the trial. To determine whether the profile of patients being enrolled in the trial is similar to that of other large, international multicenter trials that were used when estimating event rates, a novel approach is being used. The accruing demographic information in the clinical database is analyzed using the previously published TIMI Risk Score for STEMI and TIMI Simple Risk Index<sup>70, 71, 72</sup> (Figure 4).



**Figure 22 Illustration of online monitoring of profile of patients enrolled in ExTRACT-TIMI 25**

Regular updating of the risk profile of ExTRACT-TIMI 25 for the trial overall and by regions is being used by the operations committee to track the evolving nature of the enrolled population, assess whether the mortality at the end of the trial is likely to be close to that of recently completed trials that used similar enrollment criteria, and determine if any systematic change in trial design is needed. When the cohort of patients enrolled in InTIME-II was stratified by the TIMI Risk Score for STEMI and TIMI Simple Risk Index, the distribution of the scores in the trial population is as shown in the open bars in panels A and B. The profile of patients enrolled in ExTRACT-TIMI 25 when 9,651 patients were in the clinical database for the trial is shown in the overlying black squares and line graphs in the same panels. Because the position of the black squares falls very close to the height of most of the open bars in both panels, it can be deduced that the risk profile of patients in ExTRACT-TIMI 25 is similar to that of patients in InTIME-II and that the anticipated aggregate mortality for the ongoing ExTRACT-TIMI 25 trial is likely to be similar to that of InTIME-II.

The TIMI Risk Score was developed in the InTIME-II trial and was externally validated in 2 other phase 3 trials in patients with STEMI and in a large registry of patients with STEMI<sup>33</sup>. By plotting the frequency distribution of patients with various TIMI Risk Score values using bar graphs and a smoothed cumulative distribution plot, the risk profiles of populations with STEMI can be compared. The TIMI Risk Score Profile provides a means to assess whether factors other than the baseline risk of the population may be contributing to a higher- or lower-than-expected mortality. Such departures from the expected mortality may be a consequence of differences in medical therapies (including the study drugs in a clinical trial) as well as geographic or regional differences in the management of patients with STEMI. In the event that the profile of patients being enrolled in an ongoing clinical trial deviates substantially from that reported by contemporary international trials of fibrinolysis for STEMI, consideration can be given to adjustment of the enrollment criteria.

### Sub-studies

Three sub-studies aimed at providing valuable mechanistic and prognostic information were

## Clinical Review

Khin Maung U

NDA 22-138

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conducted at selected participating centers.

- **The ECG sub-study** (n = 3000) included quantitative assessment of resolution of ST-segment elevation from 12-lead electro-cardiograms (ECGs) obtained immediately before the pharmacological reperfusion regimen and 180 minutes after initiation of fibrinolysis.
- **The Cardiac Biomarker** (n = 1500) and **Genetic sub-studies** assessed the value of established (cardiac troponin, C-reactive protein, and b-type natriuretic peptide) and novel biomarkers of necrosis, inflammation, hemodynamic stress, and thrombosis for risk assessment and therapeutic decision making in patients with STEMI. Prospective validation of a multi-marker approach to risk stratification will be conducted. DNA will be obtained in selected centers from patients who will provide a separate consent for participation in the Genetic substudy.
- A pharmacoeconomic analysis using the entire trial database was performed to compare the cost-effectiveness of treatment with enoxaparin vs that with UFH. Results of the economic analysis will be reported by country and pooled across countries.

### **Study organization**

The ExTRACT-TIMI 25 trial is sponsored by Aventis Pharmaceuticals, Inc (Bridgewater, NJ) and is coordinated by the TIMI Study Group (Boston, Mass). The data were collected by a contract research organization — The raw database was provided by the sponsor to members of the TIMI Study Group. The prespecified and exploratory analyses were carried out independently by the TIMI Study Group as well as the sponsor.

b(4)

The steering committee is responsible for the scientific content of the protocol, its implementation, and the manuscript reporting the final study results.

Trial operations are coordinated by the operations committee that meets biweekly.

A CEC that does not contain any investigators participating in the study is responsible for adjudicating events in a blinded fashion.

The trial is monitored by an independent DSMB. The DSMB is assisted by an independent biostatistician who is isolated from the trial operations personnel. Recommendations from the DSMB are made to the executive committee for the trial.

Charters for the CEC and DSMB were prepared before enrollment of patients commenced. A detailed statistical analysis plan specifying the key analyses of the primary, secondary, and tertiary end points as well as additional exploratory analyses was prepared before the first formal interim analysis.

### **Protocol Amendments**

Enrollment commenced in October 2002 with a projected sample size of approximately 21000 patients. During 24-Oct-2002 through 01-Oct-2005, 20506 patients underwent randomization at 674 sites in 48 countries (9 sites in the U.S.).

There were two protocol amendments AFTER the enrollment started. The first protocol amendment was issued on 04-Dec-2002, and the second protocol amendment on 26-Aug-2004.

#### Protocol Amendment 1 (issued 04-Dec-1002):

The main changes in this amendment include:

1. Patients  $\geq 75$  years old will not receive the initial 30 mg bolus of Study Medication A (enoxaparin or matching placebo). Patients  $\geq 75$  years old will continue to receive the 0.75 mg/kg subcutaneous dose of Study Medication A as per protocol. This change is being made to reduce the risk of major bleeding or intracranial hemorrhage in the elderly.
2. Clarification that both creatine kinase (CK) and CK-MB are required to document suspected

## Clinical Review

Khin Maung U

NDA 22-138

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myocardial infarction. This change is being made to increase the accuracy of adjudication for suspected recurrent myocardial infarction.

3. The first activated partial thromboplastin time (aPTT) may be obtained 4-6 hours after randomization with another determination 6 hours later. This change is being made to reflect medical practice.
4. Introduction of three alternative systems (study sites could reduce any one) to maintain the double-blind and ensure the safety of patients. These three systems are:
  1. Encrypted Hemochron® Jr. Signature and Central Blinding Facility (no local hospital laboratory involvement);
  2. Local Hospital Laboratory and Central Blinding Facility; and
  3. Designated Medical Professional and Central Blinding Facility.

The rationale for this dose modification in patients  $\geq 75$  years old was based on safety findings of ASSENT 3 Plus trial, an open-label, multicenter, randomized (1:1, enoxaparin : UFH), controlled, parallel group trial of 1639 patients with STEMI presenting within 6 hours of symptom onset<sup>15</sup>. The ASSENT 3+ trial results, which became available in November 2002, showed that in patients  $\geq 75$  years there was a trend associated with enoxaparin for increased incidence of major bleeding (non-intracranial, 9.4% vs 5.3%) and intracranial hemorrhage (6.71% vs 0.76%), with most of these bleeding events occurring within 12 hours of randomization. This finding led to the above protocol amendment in patients  $\geq 75$  years.

#### Protocol Amendment 2 (issued 26-Aug-2004):

The Protocol Amendment 2 includes mostly clarifications, correction of minor inconsistencies and administrative changes, together with some new information. The new clinically important information (instructions to investigators) in this protocol amendment are:

1. Instructions related to coronary artery bypass graft (CABG) in a new section (Section 5.6—ExTRACT and CABG surgery).
2. Instructions related to percutaneous intervention (PCI) in a new section (Section 5.7—ExTRACT and PCI). This included:
  - Clarification on the instructions regarding non-urgent and urgent PCI, prior to and after randomization.
  - Clarification that, in case a PCI is planned during the first 8 days, every effort should be made to continue blinded study Drugs A and B until and during the PCI. This applies even if the patient is transferred for PCI, or if Drug B had been discontinued. In this later case, Drug B should be re-administered. The accompanying coagulation tests performed during the PCI should also be performed in a blinded manner.
  - Clarification that sites which do not perform PCI, should make their best effort to pre-identify preferential transfer PCI sites for optimal continuation of the double-blind, dummy study treatment.
  - Clarification that every effort should be made to collect information pertinent for the assessment of the Day 30 efficacy and safety endpoint, even if the patient has been transferred.
  - A new figure (Figure 1) was added on the administration of study Drugs A and B during PCI
  - Clarification on how to restart blinded study medication after PCI.
3. Instructions related to diagnostic catheterization in a new section, Section 5.8 (ExTRACT and diagnostic catheterization).

**Clinical Review**

Khin Maung U

NDA 22-138

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4. Clarifications on endpoints:

Ischemic endpoints: The composite endpoint of all-cause mortality, non-fatal myocardial re-infarction, and myocardial ischemia leading to urgent revascularization within 30 days after randomization became the first and main secondary objective (previously a secondary objective).

The definition of "urgent" revascularization was modified as follows: Recurrent ischemia requiring urgent revascularization is defined as any episode of recurrent myocardial ischemia at rest and/or necessitating hospitalization that leads to a revascularization procedure performed on the same hospitalization. This applies to both the index hospitalization and any hospitalization following discharge for the index event.

A definition of "rescue PCI" was added, as follows: "Rescue PCI is a PCI occurring within 8 hours of randomization, and not preceded by a recurrent ischemic event or a recurrent myocardial infarction".

It has been clarified that serial determinations of CK and CK-MB (with or without cardiac troponin) should be performed:

- At screening, 6-8 h, 12-16 h, and 18-24 h post-randomization (these measurements should be done at least 6 hours apart).
- And after revascularization procedure (at least 2 measurements within 24 hours following PCI and CABG).

It was clarified (Section 3.3) that the following ischemic events will be submitted and reviewed by the CEC for the final determination of recurrent MI:

- MI as determined by the investigator
- Prolonged ischemic discomfort at rest lasting =10 minutes, that is associated with ECG changes (as defined in Section 7.8.5 – Recurrent severe myocardial ischemia), or prompting urgent coronary revascularization, or is associated with hemodynamic decompensation.
- Database identified elevations in CK, CK-MB or troponins.

It was also clarified in Section 7.8.5 that in such cases the recurrent MI/ischemia endpoint page (page 16) of the case report form (CRF) should be faxed to — or adjudication purposes for any suspected recurrent MIs and prolonged ischemic discomfort at rest lasting 10 minutes or more that is associated with ECG changes, or prompting urgent coronary revascularization, or is associated with hemodynamic decompensation. In order to allow optimal adjudication of these events, the CRF should be promptly filled out (including the cardiac marker page of the CRF, page 5) and the relevant ECGs collected and properly labeled (with site number, kit number, and time of ECG recording). Both relevant CRF sections and ECGs will be sent promptly to the Sponsor or designee.

It was clarified that source documents for severe recurrent myocardial ischemia (not recurrent myocardial ischemia) and TIMI major hemorrhages (and not TIMI major and minor hemorrhages) will be submitted and reviewed by the CEC.

Stroke: Stroke may be diagnosed by pathologic findings consistent with ischemic or hemorrhagic stroke.

**Definitions**

KILLIP CLASS: The Killip Classification is a classification system used in individuals with an acute myocardial infarction in order to stratify them. The criteria for Killip classification include:

- Killip I: No heart failure. No clinical signs of cardiac decompensation.
- Killip II: Heart failure. Diagnostic criteria include rales, S3 gallop, and venous hypertension.

## Clinical Review

Khin Maung U  
NDA 22-138

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- Killip III: Severe heart failure. Frank pulmonary edema.
- Killip IV: Cardiogenic shock. Signs include hypotension (systolic pressure of 90 mm Hg or less) and evidence of peripheral vasoconstriction such as oliguria, cyanosis, and diaphoresis. Heart failure, often with pulmonary edema, has also been present in the majority of these patients.

The Killip classification descriptions used in the ExTRACT protocol reflect the standard language used to operationalize the original classification when conducting clinical trials.

**TIMI RISK SCORE DEFINITION:** The TIMI risk score value is a total of points defined by:

- |   |          |
|---|----------|
| • Systolic blood pressure <100 mmHg                       | 3 points |
| • Heart rate >100   | 2 points |
| • Killip II-IV  | 2 points |
| • Anterior ST elevation or left bundle-branch block       | 1 point  |
| • Diabetes, history of hypertension, or history of angina | 1 point  |
| • Weight <67 kg   | 1 point  |
| • Time to treatment >4 hours                              | 1 point  |

### Summary of results:

The ExTRACT-TIMI 25 study enrolled 20,506 patients with STEMI who were eligible for fibrinolytic therapy (at the treating physician's discretion, streptokinase [capped at 5000 patients], alteplase, tenecteplase or reteplase). The study was conducted during 24-Oct-2002 through 01-Oct-2005 at 674 sites in 48 countries including the United States (9 sites).

Of 20,506 patients randomized (10,273 enoxaparin and 10,233 UFH), 27 (17 enoxaparin and 10 UFH) did not receive study drug and had no follow-up information. Thus, the ITT population was 20,479 (10,256 enoxaparin and 10,223 UFH) patients.

In brief, patients were comparable at baseline regarding demographic and cardiovascular characteristics (Table 54). These patients had prolonged ( $\geq 20$  minutes) ischemic symptoms of rest  $\leq 6$  hours prior to randomization, the mean time ( $\pm$ SD) from symptom onset to randomization being  $3.26 \pm 7.29$  hours in the enoxaparin group, and  $3.17 \pm 1.39$  hours in the UFH group. Only 126 (1.2%) patients in enoxaparin group and 115 (1.1%) patients in UFH group were randomized  $> 6$  hours after symptom onset.

A fibrinolytic agent was administered to 99.7% patients, with 79.5% receiving a fibrin-specific agent and 20.2% (4139 patients) receiving streptokinase (Table 54). Use of fibrinolytic agent was comparable between the enoxaparin and UFH groups, being treated with streptokinase in 20.2% and 20.1%, TNK-tPA (Tenecteplase) in 19.3% and 19.6%, Reteplase in 5.5% and 5.4%, and Alteplase in 55.0% and 54.8%, respectively, of patients. 3 patients in enoxaparin group and 1 in UFH group received no fibrinolytic therapy. The median time from onset of symptoms to start of fibrinolytic therapy was 3:2 hours.

Less than 2% of treated patients did not receive the required enoxaparin/ enoxaparin placebo bolus (326 of 20,327 patients) or the required UFH/UFH placebo bolus (367 of 20,327 treated patients). The mean duration for enoxaparin/enoxaparin placebo sc injection was 6.6 days with 74.5% treated for  $\geq 6$  days (median duration = 7 days). The mean duration of UFH/UFH placebo iv infusion was 53.7 hours with 89.6% of the total population treated for  $\geq 36$  hours (median duration = 2 days).

Concomitant medications during treatment to hospitalization were comparable between the enoxaparin and UFH groups (Table 54), with aspirin in 94.8% and 95.4%,  $\beta$ -blockers (excluding eye drops) in 85.9% and 85.5%, ACE inhibitors in 78.5% and 77.8%, statins in 69.5% and 69.5%,

**Clinical Review**

Khin Maung U

NDA 22-138

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clopidogrel in 27.2% and 28.7%, oral anticoagulants in 2.1% and 2.5%, and thrombolytics (other than those of index MI) in 4% and 0.5%, respectively, of patients.

**Table 54 Baseline Characteristics of enrolled patients**

Characteristic*	Enoxaparin (N = 10,256)	UFH (N = 10,223)	P value
Age (yr)			0.35
Median	59	60	
Interquartile range	51-69	51-69	
Age ≥75 yr – no. (%)	1241 (12.1)	1291 (12.6)	0.25
Males – no. (%)	7841 (76.5)	7855 (76.8)	0.52
Caucasians – no./total no. (%)†	8935/10,255 (87.1)	8920/10,223 (87.3%)	0.79
Weight (kg)			0.22
Median	76	76	
Interquartile range	68-85	68-85	
Hypertension – no./total no. (%)	4505/10,128 (44.5)	4401/10,105 (43.6)	0.18
Hyperlipidemia – no./total no. (%)	1462/7979 (18.3)	1455/7990 (18.2)	0.85
Current smoker – no./total no. (%)	4844/10,254 (47.3)	4837/10,215 (47.4)	0.99
Diabetes mellitus – no./total no. (%)	1545/10,145 (15.2)	1515/10,104 (15.0)	0.64
Prior myocardial infarction – no./total no. (%)	1349/10,214 (13.2)	1310/10,190 (12.9)	0.46
Prior angina pectoris – no./total no. (%)	2864/10,179 (28.1)	2851/10,166 (28.0)	0.88
Prior PCI – no./total no. (%)	340/10,244 (3.3)	320/10,217 (3.1)	0.45
Anterior MI – no./total no. (%)	4439/10,176 (43.6)	4494/10,157 (44.2)	0.37
Long-term aspirin treatment – no./total no. (%)	1396/10,213 (13.6)	1356/10,205 (13.3)	0.45
UFH within 3 h before randomization – no./total no. (%)	1634/10,255 (15.9)	1608/10,223 (15.7)	0.69
LMWH within 7 days before randomization – no./total no. (%)	43 (0.4)	50 (0.5)	0.46
Creatinine clearance (ml/min)			0.23
Median	82.3	82.0	
Interquartile range	63.6-104.6	63.1 – 104.2	
Killip Class – no. (%)			0.92
I	9098 (88.8)	9078 (88.8)	
II	1049 (10.2)	1036 (10.1)	
III	94 (0.9)	99 (1.0)	
IV	6 (0.1)	8 (0.1)	
Data missing	9 (0.1)	2 (<0.1)	
TIMI risk score – no./total no. (%)‡			0.84
≤3	6534/10,139 (64.4)	6519/10,113 (64.3)	
>3	3605/10,139 (35.6)	3618/10,137 (35.7)	
Time from symptom onset to start of fibrinolytic therapy – hr			0.65
Median	3.1	3.2	
Interquartile range	2.2 – 4.3	2.2 – 4.3	
Fibrinolytic therapy – no. (%)			0.91
Tenecteplase	1976 (19.3)	2010 (19.7)	
Alteplase	5605 (54.7)	5570 (54.5)	
Retepase	561 (5.5)	561 (5.5)	
Streptokinase	2083 (20.3)	2056 (20.1)	
None	31 (0.3)	26 (0.3)	
Time from fibrinolytic therapy to study drug administration – no./total no. (%)‡			0.09
0-15 min	1216/10,157 (12.0)	1140/10,144 (11.2)	
0-30 min	8604/10,157 (84.7)	8677/10,144 (85.5)	
>30 min	310/10,157 (3.1)	286/10,144 (2.8)	
Cardiac medications during index hospitalization – no. (%)			
Aspirin	9727 (94.8)	9749 (95.4)	0.08
Clopidogrel	2788 (27.2)	2939 (28.7)	0.01
β-blockers	8811 (85.9)	8745 (85.5)	0.45
ACE inhibitors or angiotensin-receptor blockers	8208 (80.0)	8109 (79.3)	0.21
Statin	7124 (69.5)	7103 (69.5)	0.98

\*LMWH = low molecular weight heparin; ACE = angiotensin-converting enzyme; † Race was self-reported; ‡ The TIMI risk score was based on the results for 10,139 patients in the enoxaparin group and 10,137 patients in the UFH group. Higher scores indicate higher risk.

In summary, the ExTRACT-TIMI 25 trial showed that enoxaparin significantly (p=0.000003)

## Clinical Review

Khin Maung U

NDA 22-138

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reduced the incidence of the composite primary efficacy endpoint (all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group vs 12% in the UFH group, 17% relative risk reduction).

This benefit is contributed mainly by a significant reduction in the incidence of non-fatal myocardial re-infarction (3.0% in enoxaparin group vs 4.5% in UFH group, 33% relative risk reduction,  $p < 0.001$ ), whereas the reduction in mortality (6.9% in enoxaparin group vs 7.5% in UFH group, 8% relative risk reduction) was not statistically significant ( $p = 0.11$ ).

The time-to-composite-endpoint (of death or recurrent nonfatal MI) also showed a statistically significant reduction in the enoxaparin group compared to the UFH treatment group (HR = 0.83, 95% CI 0.77 – 0.90,  $P < 0.001$ ).

The treatment benefit of enoxaparin became evident at 48 hours, and was significantly positive at Day 8 and at Day 30.

This clinical benefit of treatment with enoxaparin was consistently demonstrated:

- across pre-specified subgroups of
  - age (<75 years vs  $\geq 75$  years),
  - infarct location,
  - presence of prior MI,
  - presence of diabetes mellitus,
  - presence of severe renal function impairment,
  - treatment with PCI or medical treatment,
  - type of fibrinolytic agent used,
  - concomitant medications with the exception of non-use of  $\beta$ -blockers, and
  - severe heart failure or cardiogenic shock (Killip Class III/IV),
- as positive findings when either myocardial ischemia leading to urgent revascularization or disabling stroke were added to the primary efficacy endpoint (first and main secondary efficacy and other secondary efficacy endpoints), and
- as positive findings in the tertiary composite endpoints.

This clinical benefit produced by enoxaparin appears to be limited to 30 days post-randomization. In the ExTRACT-TIMI 25 study, the Kaplan-Meier curves for death up to 12 months post-randomization for enoxaparin and UFH run closely together. This observation was also found in the long-term results of the ASSENT 3 study. Despite the separation of the survival curves over 12 months for (a) death and myocardial re-infarction, and (b) death, myocardial re-infarction and disabling stroke, an analysis of clinical events at 6- and 12- months showed an excess of deaths and myocardial re-infarction when (1) deaths are day 30 post-randomization were excluded, and (2) patients who experienced the composite primary efficacy endpoint (death or myocardial re-infarction) were excluded.

The ExTRACT-TIMI 25 study provided safety data for 20,327 patients with STEMI (enoxaparin: 10,176 patients; UFH: 10,151 patients) who received at least one dose of study treatment. The primary safety endpoint was TIMI major hemorrhage within 30 days after randomization. The Fisher's Exact test was used to evaluate differences between the treatment groups for this primary safety endpoint.

The majority (82%) of patients in each group completed the assigned treatment regimen. 17.6% (1790 of 10,256) patients in enoxaparin group and 18% (1830 of 10,223) patients in UFH group discontinued; most frequently due to a hemorrhagic AE (34.1% in enoxaparin group vs 24% in UFH group) or PCI-related reasons (48.5% (128 of 525) patients in enoxaparin group and 51.5% (136 of 625) patients in UFH group).

## Clinical Review

Khin Maung U

NDA 22-138

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The sponsor also provided safety data for 10,040 randomized patients with STEMI (4128 enoxaparin patients, 5673 UFH patients, and 239 placebo patients) from 6 previously conducted studies. A majority (58%) of patients in each of the 6 studies completed the assigned treatment. Hemorrhagic events were the most frequent AEs that resulted in treatment discontinuation in all of these studies.

The safety findings in the ExTRACT-TIMI 25 study were as follows:

- Enoxaparin was associated with an *increase* in adjudicated TIMI major bleeding compared with UFH in patients with STEMI (2.1% vs 1.4%,  $p < 0.0001$ ).
- No statistical difference ( $p = 0.1443$ ) was detected in ICH between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).
- The non-hemorrhagic AEs were similar between treatment groups.
- The results of subgroup analyses for the primary safety endpoint in the ExTRACT study did not identify treatment by subgroup interactions.

When the balance of efficacy and safety was assessed using 3 net clinical benefit composite endpoints of:

- death/re-infarction/nonfatal disabling stroke,
- death/re-infarction/ nonfatal major bleeding, and
- death/re-infarction/non-fatal ICH,

the incidence of events for each of the composite endpoints was significantly ( $P < 0.001$  for all comparisons) lower at 30 days in the enoxaparin group compared with the UFH group. Reductions in the absolute event rates of 1.8 to 2.2 percentage points corresponded to relative risk reductions ranging from 14% to 18%, supporting the overall positive effect of enoxaparin on both efficacy and clinically important safety endpoints.

Thus, despite an increase in episodes of TIMI major bleeding, the early and sustained reduction in ischemic events and the net positive balance of efficacy and safety endpoint events demonstrated the beneficial effect of the regimen of enoxaparin as the adjunctive antithrombin regimen in patients with STEMI treated medically and with fibrinolytic therapy, whether or not they underwent subsequent PCI.

The net clinical benefit favored enoxaparin-treated patients: for every 1000 STEMI patients treated with enoxaparin, there would be

- 6 fewer deaths,
- 15 fewer nonfatal myocardial re-infarctions and
- 7 fewer episodes of urgent revascularization,

at a cost of an increase of 4 non-fatal major bleeds, with no increase in the number of non-fatal intracranial hemorrhage.

### 10.1.2 Review of the 6 previous studies

Design of the 6 previous studies (please also see Table 2 and Table 3):

There were also 6 previous studies conducted between 1995 and 2005, which enrolled an additional 10,171 patients with STEMI. Of these:

- ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23, and HART II were *open-label* studies, and
- AMI-SK and TETAMI studies were *double-blind, placebo-controlled* studies, of which
  - AMI-SK study evaluated reperfusion (TIMI flow grade 3) by angiography, and
  - TETAMI study enrolled *non-thrombolized* patients with STEMI (i.e., *STEMI patients*)

## Clinical Review

Khin Maung U

NDA 22-138

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*ineligible for reperfusion*) only, and showed that enoxaparin did *not* reduce the 30-day incidence of death, reinfarction and recurrent angina significantly compared with UFH in non-reperused STEMI patients.

The inclusion criteria for the 6 previous studies were similar: male and female patients  $\geq 18$  years old (21 years old for the ENTIRE study, and in Argentina for the AMI-SK study), with ischemic symptoms  $\geq 30$  minutes within 6 to 24 hours prior to randomization, and ECG evidence of ST-segment  $> 0.1$  mV in at least 2 limb leads. The TETAMI, ASSENT 3 and ASSENT 3+ studies also accepted patients with ECG evidence of left bundle-branch block.

The treatment duration for enoxaparin in these studies ranged from 3 to 8 days or until hospital discharge (whichever came first), and that for UFH ranged from 48 to 72 hours.

The enoxaparin and UFH treatment regimens differed across studies due to the absence of an initial enoxaparin iv bolus or to the addition of a fibrinolytic medication administered either prior to and/or following enoxaparin sc administration. However, at least one treatment arm of these regimens was generally consistent with the ExTRACT study – i.e., the dosing regimen for enoxaparin in patients  $< 75$  years old (i.e., 30 mg iv bolus followed by 1 mg/kg sc twice daily until hospital discharge or up to Day 8). 2923 patients received enoxaparin at this dosing regimen in the 6 previous studies; however, only 453 of these patients participated in studies designed specifically to investigate the 30 mg iv bolus plus 1 mg/kg sc twice daily enoxaparin dosing regimen (HART II and AMI-SK studies).

A clinically important difference between the ExTRACT-TIMI 25 study and the 6 previous studies is that in the latter, enoxaparin was administered without dose modifications for age or renal impairment.

Concomitant medications received by patients were similar across these studies: patients on aspirin received an initial dose of aspirin (150 to 325 mg), and then a daily maintenance dose of 75 to 325 mg. Additional therapy for cardiac ischemia was administered at the Investigator's discretion.

In the HART II study, patients received a 15 mg iv bolus of recombinant tissue plasminogen activator (rt-PA), followed by 0.75 mg/kg iv for 30 min (to a maximum of 50 mg), and 0.50 mg/kg iv for 60 min (to a maximum of 35 mg). In the AMI-SK study, patients received iv streptokinase (1.5 million units over 60 min) prior to receiving the study drug.

Due to differences in study designs and endpoints, no integrated analyses were performed on the efficacy data from the ExTRACT-TIMI 25 study and the 6 previous studies.

### 10.1.2.1 ASSENT 3 (ASSessment of the Safety and Efficacy of New Thrombolytic regimens) Study:

*A phase IIIb, randomized, open label trial with 3 parallel groups: full dose tenecteplase together with heparin sodium; full dose tenecteplase together with enoxaparin; and half dose tenecteplase together with abciximab and heparin sodium in patients with acute myocardial infarction.*

This was a randomized, open-label, multicenter, international trial of 3 parallel groups at 575 centers. The objective was to evaluate the safety and efficacy of full dose tenecteplase with UFH, full dose tenecteplase combined with enoxaparin, and half dose tenecteplase combined with abciximab and UFH.

The study enrolled patients  $\geq 18$  years with onset of acute MI within 6 hours prior to randomization, shown by ST-segment elevation  $\geq 0.1$  mV in 2 or more limb leads or  $\geq 0.2$  mV in 2 or more contiguous precordial leads or left bundle-branch block.

The study enrolled 6116 patients; 6095 were randomized (ITT) and 5989 were treated with a study

**Clinical Review**

Khin Maung U

NDA 22-138

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drug. The primary efficacy endpoint was a composite of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia. The primary efficacy and safety mixed composite endpoint was 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital intracranial hemorrhage (ICH) or in-hospital major bleedings (other than ICH).

**Efficacy Findings:** At 30 days, full dose tenecteplase plus enoxaparin, and half-dose tenecteplase plus abciximab regimens significantly reduced the primary efficacy and primary efficacy and safety composite endpoints (Table 55 and Table 56). However, 30-day mortality reduction alone was not significantly different among the three groups. Subgroup analyses showed that the combination containing abciximab seemed harmful for diabetics and elderly patients.

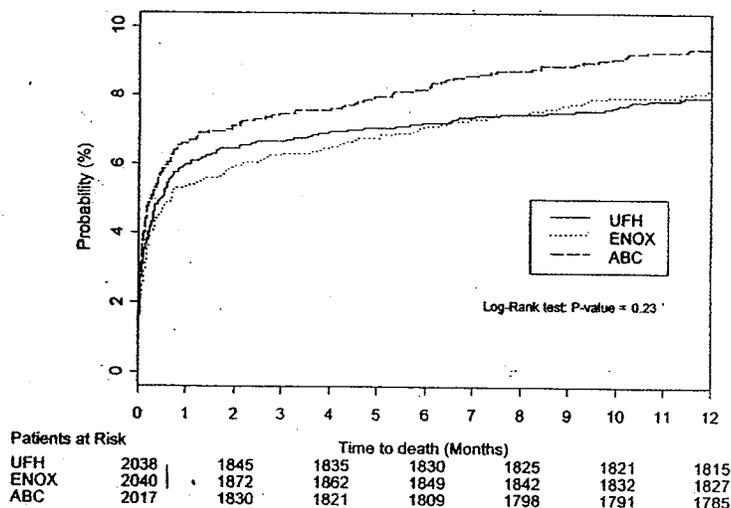
**Table 55 Primary efficacy composite endpoint at 30 day in ASSENT 3 study (ITT)**

	<u>Event rate</u>	<u>95% C.I.</u>
UFH	314/2038 (15.4 %)	13.92, 17.06
Enoxaparin	233/2037 (11.4 %)	10.14, 12.91
Abciximab	223/2017 (11.1 %)	9.77, 12.51
Overall test	p = 0.0001	

**Table 56 Primary efficacy plus safety composite endpoint at 30 day in ASSENT 3 study (ITT)**

	<u>Event rate</u>	<u>95% C.I.</u>
UFH	347/2036 (17.0 %)	15.49, 18.76
Enoxaparin	280/2037 (13.8 %)	12.33, 15.3
Abciximab	287/2016 (14.2 %)	12.79, 15.851
Overall test	p = 0.0081	

**Figure 23 ASSENT 3 Study: Kaplan-Meier Curve for 1-year mortality (ITT population)**



At one year, there was no significant difference in mortality (Figure 23). The one-year mortality curves diverge in the first month, after which the mortality curves for patients with enoxaparin or abciximab run in parallel, with abciximab associated with a higher 1-year mortality rate (log rank test, p=0.226); the curve for UFH crosses the enoxaparin curve between 7 and 8 months after randomization, resulting in similar mortality rates at 1 year after randomization. No significant subgroup differences were found.

**Safety Findings:** The regimen containing abciximab showed significantly increased risk for major

**Clinical Review**

Khin Maung U

NDA 22-138

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bleeds (other than ICH and thrombocytopenia) (Table 57).

**Table 57 Assent 3 Study: Clinically important adverse events in-hospital (ITT population)**

Adverse event (In-hospital)	Group A (N = 2038) (%)	Group B (N = 2040) (%)	Group C (N = 2017) (%)	p-value (overall)
ICH	0.93	0.88	0.94	0.9770
Stroke	1.52	1.62	1.49	0.9417
Major bleeds (excl. ICH)	2.16	3.04	4.32	0.0004
Minor bleeds	18.77	22.55	35.37	< 0.0001
Blood transfusions	2.31	3.43	4.16	0.0032
Serious thrombocytopenia	0.20	0.10	0.59	0.0101
Any thrombocytopenia	1.32	1.18	3.17	< 0.0001

**Conclusion:** The combination of full-dose tenecteplase and enoxaparin seems to be the best treatment arm in this trial: it provided significant reduction in the composite primary efficacy endpoint of 30-day mortality, in-hospital reinfarction or in-hospital refractory ischemia, ease of self-administration, lack of need for anticoagulation monitoring, and intermediate safety issues (compared to the regimen containing abciximab).

#### 10.1.2.2 ASSENT 3+ (Assessment of the Safety and Efficacy of New Thrombolytic regimens) Study:

*A phase IIIb-IV, randomized, open label trial on efficacy and safety of 2 parallel groups: full dose tenecteplase together with UFH sodium or enoxaparin in acute myocardial infarction in the pre-hospital setting. This study is a satellite study to ASSENT 3 (main study).*

This was a randomized, open-label, multicenter, international trial at 88 centers. The objective was the same as ASSENT 3 Study: to evaluate the safety and efficacy of full dose tenecteplase with UFH and full dose tenecteplase combined with enoxaparin. The inclusion criteria were also similar to ASSENT 3 Study.

The study randomized 1639 patients (ITT), and 1606 were treated with a study drug. The composite primary efficacy endpoint and primary efficacy and safety mixed composite endpoint were the same as the ASSENT 3 Study.

**Efficacy Findings:** The primary efficacy and efficacy plus safety endpoints were not significantly different at 30 days (Table 58 and Table 59) although the event rates were lower for Enoxaparin.

**Table 58 Primary efficacy composite endpoint at 30 day in ASSENT 3+ Study (ITT)**

	Event rate	95 % C.I.
UFH	142/818 (17.4 %)	14.76, 19.96
Enoxaparin	116/817 (14.2 %)	11.80, 16.59
P value	p = 0.080	

**Table 59 Primary efficacy plus safety composite endpoint at 30 day in ASSENT 3+ Study (ITT)**

	Event rate	95 % C.I.
UFH	166/818 (20.3 %)	17.54, 23.05
Enoxaparin	149/816 (18.3 %)	15.61, 20.91
P value	p = 0.297	

There was no significance difference between treatment groups for 30 day mortality (Table 60). The lower event rate of the primary efficacy composite appears to be contributed mainly by a significant reduction in reinfarction (Table 61) and a reduction in refractory ischemia (Table 62).

**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)**Table 60 30-day mortality (ITT)**

	<u>Event rate</u>	<u>95 % C.I.</u>
UFH	49/818 (5.99%)	4.36, 7.62
Enoxaparin	61/817 (7.47%)	5.66, 9.27
P value	p = 0.080	

**Table 61 In-hospital reinfarction (ITT)**

	<u>Event rate</u>	<u>95 % C.I.</u>
UFH	48/821 (5.8 %)	4.24, 7.45
Enoxaparin	29/818 (3.5 %)	2.28, 4.81
P value	p = 0.080	

**Table 62 In-hospital refractory ischemia (ITT)**

	<u>Event rate</u>	<u>95 % C.I.</u>
UFH	53/821 (6.5 %)	4.77, 8.14
Enoxaparin	36/818 (4.4 %)	3.00, 5.81
P value	p = 0.066	

**Safety Findings:** Stroke and ICH occurred significantly more often in Enoxaparin group (Table 63), with most ICH occurring early after starting treatment (72% (13/18) of ICHs in enoxaparin group compared to only 37% (3 of 8) in UFH group). ICH and strokes were increased in patients >75 years. For stroke at 30 days, the rate in the elderly was 9.40% in enoxaparin group compared to 2.27% in UFH group. In-hospital ICH rate did not change with age for UFH group (1.02% vs 0.76%), but in the enoxaparin group, ICH rate showed a large increase with age (1.20% vs 6.71% for patients ≤75 years and >75 years, respectively).

**Table 63 Assent 3+ Study: Clinically important adverse events in-hospital (ITT population)**

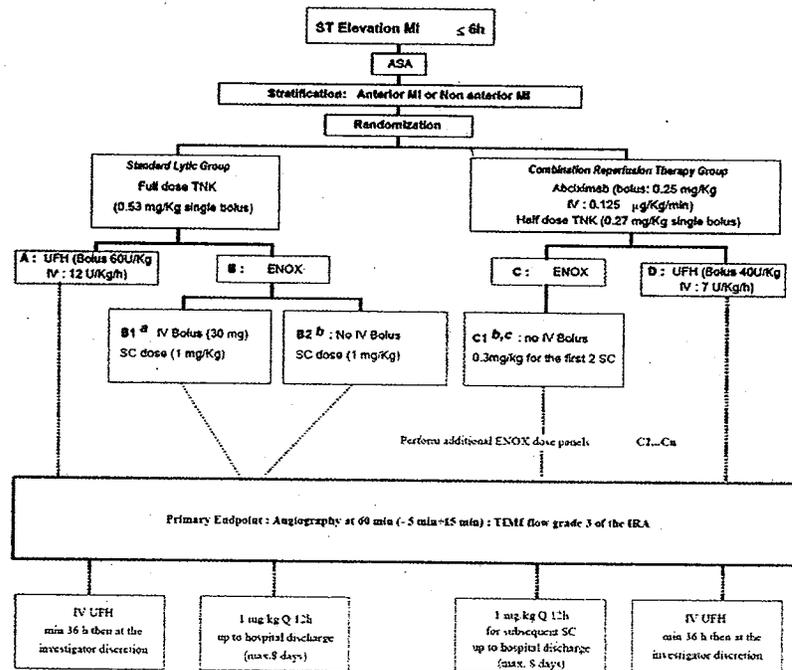
Adverse event (In-hospital)	Group A n/N %	Group B n/N %	p-value
ICH	8/821 0.97%	18/818 2.20%	0.047
Stroke	11/821 1.34%	24/818 2.93%	0.026
Major bleeds (excl. ICH)	23/821 2.80%	33/817 4.04%	0.176
Minor bleeds	198/821 24.12%	237/817 29.01%	0.025
Thrombocytopenia (any)	6/821 0.73%	9/818 1.10%	0.452

**Conclusion:** Enoxaparin reduced, albeit not statistically significantly, the composite primary efficacy endpoint of 30-day mortality, in-hospital reinfarction or in-hospital refractory ischemia in patients with STEMI. However, enoxaparin treatment was associated with an increased risk of major bleeding (ICH and stroke), particularly in patients >75 years old. This study provided the basis for dose adjustment for elderly patients in the main pivotal ExTRACT-TIMI 25 study.

### 10.1.2.3 ENTIRE Study

*A Phase II stratified, randomized, open-label, angiographic trial to assess the safety and efficacy of enoxaparin as an adjunct to thrombolytic with or without GPIIb/IIIa therapy in subjects with ST elevation MI.* The doses and design of the ENTIRE Study are shown in Figure 24.

Figure 24 Design of ENTIRE-TIMI 23 Study



This was a stratified (anterior/non-anterior MI), multi-center study in 43 centers, with 10 centers in the US, 2 in Canada, 5 in Belgium, 7 in France, 11 in the Netherlands and 8 in Spain. The study had a dose-finding phase followed by a dose-confirmation phase. Patients were randomized to be treated with either UFH (groups A and D) for  $\geq 36$  hours or enoxaparin (groups B and C) up to 8 days or hospital discharge (whichever came first) unless a prior successful PCI was performed.

The objectives of the study were:

- To find the dose of enoxaparin that, in combination with half-dose tenecteplase (TNK-tPA) (0.27 mg/kg) and with full-dose abciximab (bolus 0.25 mg/kg, infusion 0.125 µg/kg/minute x 12 hours), was associated with a TIMI grade 3 flow at 60 minutes in at least 60% of subjects;
- To demonstrate that, in subjects with STEMI receiving a reperfusion regimen of full dose TNK-tPA (0.53 mg/kg), adjunctive therapy with enoxaparin was associated with a TIMI grade 3 flow at 60 minutes in at least 45% of subjects; and
- To assess the safety of enoxaparin as adjunctive therapy with various reperfusion regimens.

The study enrolled patients  $\geq 21$  to 75 years with prolonged ( $\geq 30$  min) ischemic symptoms  $\leq 6$  hours prior to randomization, and ST-segment elevation  $\geq 0.1$  mV in 2 or more limb leads or  $\geq 0.2$  mV in 2 or more contiguous precordial leads or left bundle-branch block.

The primary efficacy endpoint was the evaluation of TIMI 3 flow grade in the infarct related artery (IRA) at 60 minutes post-TNK-tPA bolus. Angiography was performed at 50 min (-5 min to +15 min) post-TNK-tPA administration. A core laboratory analyzed the TIMI flow. A population

## Clinical Review

Khin Maung U

NDA 22-138

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pharmacokinetic study (anti-Xa and anti-IIa activities) was performed at selected centers.

**Efficacy Findings:** 488 patients were randomized, 483 patients received treatment with study medication. For the primary efficacy analysis, 415 patients had an evaluable angiogram performed between 55 and 75 minutes from administration of TNP-tPA.

The primary objective to reach 60% of patients with TIMI grade 3 flow at 60 min in the Combination Reperfusion Therapy group was not met in either enoxaparin or UFH group. The study showed no difference in TIMI grade 3 flow between treatment groups, whether treated with Standard Lytic Therapy (full dose TNK-tPA) or Combination Reperfusion Therapy (Abciximab plus half dose TNK-tPA). The pooled rate of TIMI grade 3 flow as 50.9% (140 of 275 patients) with enoxaparin and 50% (70 of 140 patients) with UFH (Table 64).

**Table 64 Summary of 60-minute angiography results – core lab assessment in the ENTIRE study – Evaluable population**

Parameter	Number (%) of patients	
	Enoxaparin N = 275 (%)	UFH N = 140 (%)
TIMI flow grade		
0	45 (16.4)	31 (22.1)
1	17 (6.2)	4 (2.9)
2	73 (26.5)	35 (25.0)
3	140 (50.9)	70 (50.0)
TIMI flow grade 2 + 3	213 (77.5)	105 (75.0)

N = population size; UFH = unfractionated heparin; TIMI = Thrombolysis in Myocardial Infarction  
Source: Sponsor's Table 30 in Summary of Clinical Efficacy p 52.

The composite of death or MI was significantly ( $P=0.005$ ) higher with UFH (15.9%) than with enoxaparin (4.4%) in patients in the Standard Lytic group, while it was not different in the Combination Reperfusion Therapy group treated with UFH (6.5%) and enoxaparin (5.5%).

**Safety Findings:** Data on 483 patients who received treatment with study drug was reported. Among patients receiving Standard Lytic Therapy, TIMI major hemorrhages were fewer with enoxaparin compared to UFH. In the Combination Reperfusion Therapy group, TIMI hemorrhages were more frequent with enoxaparin (8.5%) compared to UFH (5.2%); when PCI was performed, the rates of TIMI major hemorrhages were similar for the UFH (7.7%) and enoxaparin (8.0%) treatment groups.

The most frequently reported TIMI major hemorrhages were (i) ecchymosis/hematoma >5 cm at sheath site (5.6%, 6 of 108), and (ii) intracerebral hemorrhage (4.6%, 5 of 108).

**Conclusion:** The primary objective to reach 60% of patients with TIMI grade 3 flow at 60 min in the Combination Reperfusion Therapy group was not met in either enoxaparin or UFH group. The risk of major hemorrhages in the Standard Lytic Therapy group was similar.

### 10.1.2.4 HART II Study

*An open-label, randomized, parallel, multicenter trial comparing the safety and efficacy of subcutaneous enoxaparin to intravenous unfractionated heparin as an adjunct to thrombolytic therapy in patients presenting with acute myocardial infarction.*

This was a multi-center study in 23 centers in 3 countries, with 8 centers in the US, 5 in Canada, and 10 in the Netherlands. The study enrolled patients  $\geq 18$  years with ischemic symptoms lasting

**Clinical Review**

Khin Maung U

NDA 22-138

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between 30 min and 12 hours, and ST-segment elevation > 0.1 mV in 2 or more limb leads or > 0.2 mV in 2 or more contiguous precordial leads.

Patients received rt-PA by intravenous bolus (15 mg), followed by infusion of 0.75 mg/kg for 30 minutes and 0.50 mg/kg for 60 minutes (maximum dose = 100 mg) (Front-loaded method). At the start of rt-PA, patients also received enoxaparin by iv bolus (30 mg), followed by 1.0 mg/kg sc every 12 hours (up to 72 hours) OR UFH by iv bolus (4000 - 5000 units), followed by infusion of 15 units/kg/hour for 77 hours and adjusted based on aPTT.

The primary efficacy endpoint was TIMI grade 2 or 3 flow at 90 minutes in the IRA post rt-PA angiography and the re-occlusion assessment at the 5 to 7 days angiography. Angiographic parameters were assessed by a core laboratory. The primary efficacy analysis was a between group comparison of reperfusion rate of the IRA at the 90 minute post rt-PA angiogram (TIMI flow grade 2-3) using "all randomized and assessed population."

Clinical endpoints (death - reinfarction – recurrent ischemia) were collected up to Day 30.

Safety was evaluated by the incidence of major hemorrhages (by Aventis definition and TIMI classification) including hemorrhagic stroke, up to Day 30.

**Efficacy Findings:** A total of 295 (77.6%) randomized and assessed patients (80.1% and 75.1% of the enoxaparin and UFH groups, respectively) presented an initial TIMI grade 2 or 3 flow at 90 minutes. Initial TIMI flow was grade 3 for 52.9% of enoxaparin patients and for 47.6% of UFH patients. The absolute difference in occurrence of TIMI grade 2 or 3 flow between groups was 5.0%. Thus, the one-sided lower limit of 95 % CI was -2.1%, far from the -10% non-inferiority limit and close to the superiority limit (0). The non-inferiority hypothesis was, therefore, confirmed (two-sided 95% CI was -3.4% to 13.3%). No treatment-by-center interaction was found for these results (p = 0.797). Table 31 shows the results of the 90-minute angiography for the all-randomized and assessed population.

**Table 65 Results of the 90-minute angiography in the HART II study – all-randomized and assessed population**

	Treatment group	
	Enoxaparin N=191 (%)	UFH N=189 (%)
Initial TIMI Flow: primary parameter		
0	30 (15.7)	37 (19.6)
1	8 (4.2)	10 (5.3)
2	52 (27.2)	52 (27.5)
3	101 (52.9)	90 (47.6)
Initial TIMI Flow (combined grades)		
0+1	38 (19.9)	47 (24.9)
2+3	153 (80.1)	142 (75.1)

Time from rt-PA bolus administration; N = population size; UFH = unfractionated heparin; TIMI= Thrombolysis in Myocardial Infarction; Source: Sponsor's Table 31 in Summary of Clinical Efficacy p 53.

By Day 30, there was no difference in the frequencies of each clinical endpoint (death, reinfarction, recurrent ischemia), and combined double and triple endpoints between treatment groups.

**Safety Findings:** Fifty-one (51) patients (13.0%) presented with Aventis major hemorrhages by Day 30 (13.3% enoxaparin, 12.7% heparin, p= 0.88). The majority of these hemorrhages occurred by Day 3 (44 patients). The most frequent site of major hemorrhage in both treatment groups was sheath site hematoma (26 (6.6%) patients (14 enoxaparin, 12 heparin patients)).

## Clinical Review

Khin Maung U

NDA 22-138

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Fourteen (14) patients (3.6%) presented TIMI major hemorrhages by Day 30 (8 enoxaparin, 6 heparin patients) most of which occurred up to Day 3, and was comparable between groups.

The incidence of non-hemorrhagic AEs, reported in 269 patients during hospitalization, was comparable between groups. Most of the events were related to the cardiovascular system (171 patients).

110 patients presented at least one non-hemorrhagic SAE by Day 30, most of them occurring up to Day 3 (74 patients). 99 were related to the cardiovascular system (mostly angina pectoris, myocardial ischemia or infarction, and ventricular fibrillation).

Fifty four (54) patients were discontinued because of AEs, mostly hemorrhages.

Of the six (6) strokes which occurred up to Day 30 (4 enoxaparin and 2 heparin patients), 4 were considered to be hemorrhagic strokes (2 enoxaparin and 2 heparin patients).

Nineteen (19) patients died up to Day 30 (9 enoxaparin and 10 heparin patients). Most deaths were due to cardiovascular causes.

**Conclusion:** The study showed that enoxaparin is equivalent to UFH in the improvement of TIMI flow through IRAs of patients with acute MI treated with rt-PA. In addition, enoxaparin appears to show a lower rate of re-occlusion than UFH.

No significant differences were observed between enoxaparin and unfractionated heparin for the occurrence of hemorrhages or adverse events.

### 10.1.2.5 The AMI-SK Study

*The safety and efficacy of subcutaneous enoxaparin and streptokinase in patients presenting with acute myocardial infarction: an international, double-blind, placebo-controlled, randomized, parallel group, multicenter study*

This was a double-blind, placebo-controlled, randomized, parallel-group, multicenter study at 37 centers in 5 countries (Canada= 4 centers, Germany= 6 centers, Hungary= 6 centers, Poland= 8 centers and Spain= 13 centers), to evaluate the efficacy and safety of enoxaparin versus placebo, as adjunct to streptokinase therapy (Dose = 1.5 million units over 60 minutes).

The study enrolled patients >18 years old with a suspected Q-wave myocardial infarction in the previous 12 hours defined as ischemic discomfort lasting > 30 minutes within 12 hours of enrollment and a 12-lead electrocardiogram (ECG) with an ST-segment > 0.1 mV in 2 or more limb leads, or > 0.2 mV in two or more contiguous precordial leads, indicative of acute MI. Patients were treated for 3-8 days with either enoxaparin (iv bolus of 30 mg followed by 1.0 mg/kg sc q 12 h for 3 to 8 days) or placebo. Angiography was performed at Day 8 (range 5-10) and the patients were followed-up to Day 30. Clinical efficacy and safety endpoints were adjudicated by a CEC.

The primary efficacy objective was to assess the efficacy of enoxaparin as an adjunctive therapy to streptokinase (SK), measured by the infarct related artery patency rate (TIMI flow grade 3) at Day 8. The primary efficacy endpoint was TIMI flow grade (0 to 3) on angiography performed at Day 8 (range 5 to 10 days). In addition, ST-segment resolution on ECG at 90 and 180 minutes, incidence of clinical endpoints, revascularization procedures (up to Day 30), and infarct size were also evaluated. Angiography, electrocardiograms and infarct size were assessed by core laboratories.

The primary safety endpoint was the incidence of major hemorrhages (by Aventis definition) including hemorrhagic stroke, up to Day 30. In addition, the incidence of any hemorrhages, non-hemorrhagic adverse events and laboratory abnormalities (hemoglobin levels and platelet counts) were evaluated.

**Clinical Review**

Khin Maung U

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**Efficacy Findings:** The primary analysis on 389 evaluable patients (Table 66) showed that significantly ( $p = 0.010$ ) more enoxaparin patients (70.3%; 142 of 202 patients) presented a TIMI flow grade 3, compared to placebo (57.8%; 108 of 187 patients).

**Table 66 Day 8 angiography results per core laboratory in the AMI-SK study – Evaluable population**

	Treatment group	
	Enoxaparin N=202 (%)	Placebo N=187 (%)
TIMI Flow:		
0	17 ( 8.4%)	42 ( 22.5%)
1	8 ( 4.0%)	11 ( 5.9%)
2	35 ( 17.3%)	26 ( 13.9%)
3	142 ( 70.3%)	108 ( 57.8%)
TIMI Flow:		
0+1	25 ( 12.4%)	53 ( 28.3%)
2+3	177 ( 87.6%)	134 ( 71.7%)

TIMI = Thrombolysis in Myocardial Infarction; Source: Sponsor's Table 32 in Summary of Clinical Efficacy p 53.

Significantly more patients presented ST-segment resolution at 90 minutes ( $p = 0.012$ ) and 180 minutes post-streptokinase ( $p = 0.04$ ) in the enoxaparin group than in the placebo group.

By Day 30, there were significantly less patients ( $p = 0.03$ ; relative risk reduction = 36%) presenting a triple-endpoint in the enoxaparin group (13.4%) compared to the placebo group (21.0%).

Regarding the single endpoints, the largest difference was found in the rate of recurrent MI ( $p = 0.01$ ).

There was no significant difference between treatment groups for the incidence of revascularization (68 [28.0%] placebo patients and 75 [29.6%] enoxaparin patients). No differences were observed with regard to the infarct size.

**Safety Findings:** The most frequent types of major hemorrhages (causing a decrease in hemoglobin of  $\geq 3$  g/dl) were hematomas  $> 5$  cm at the injection site or at the sheath site, or gastrointestinal hemorrhages. No major hemorrhage led to death. Using the TIMI definition, TIMI major hemorrhages were reported in 1.6% of enoxaparin patients and 0.8% of placebo patients, and TIMI minor hemorrhages occurred in 2.4% of enoxaparin patients, and 1.3% of placebo patients.

By Day 30, there was a significantly ( $p = 0.010$ ) higher number of enoxaparin patients (23.0%) presenting any hemorrhagic episode, compared to placebo (14.2%). The majority of hemorrhagic episodes occurred within the first 3 days. Most of the hemorrhages occurring by Day 30 were considered to be minor hemorrhages and were mostly ecchymoses or hematomas at injection site.

There were 3 non-hemorrhagic strokes and the one hemorrhagic stroke; all occurred in the placebo group.

Thirty-four (34) patients had died by Day 30 (17 enoxaparin patients and 17 placebo patients).

Thirty (30) patients withdrew because of an adverse event. Of these, 17 patients (15 [6%] enoxaparin patients and 2 [0.8%] placebo patients) withdrew because of hemorrhagic episodes.

One-hundred-and-fifty-seven (157) patients presented at least one non-hemorrhagic adverse event by Day 30, mostly related to the cardiovascular system (131 events, with no significant difference between treatment groups ( $p > 0.05$  for all events with a 1 % rate of incidence).

Seventy-two (72) patients presented a serious adverse event (SAE) by Day 30: 20 presented serious hemorrhages (13 [5.2%] enoxaparin patients and 7 [2.9%] placebo patients). Sixty (30 in each group) presented non-hemorrhagic SAE mostly related to the cardiovascular system.

## Clinical Review

Khin Maung U

NDA 22-138

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**Conclusions:** The AMI-SK study indicates that in patients with STEMI thrombolized with streptokinase, adjunctive therapy with enoxaparin improves early coronary reperfusion and reduces the risk of re-occlusion, as shown by a reduction in clinical events, particularly re-infarction and better coronary patency at the 5-10 day coronary angiography, which was the primary study endpoint. In addition, improved early coronary reperfusion is suggested by greater resolution of the ST-segment elevation as analyzed at 90 and 180 minutes.

A significantly higher number of hemorrhages was observed in enoxaparin patients; the majority of them were considered minor. No hemorrhagic stroke occurred in enoxaparin patients and there was no significant increase in the risk of major bleeding. However, the safety profile and the benefit risk ratio of enoxaparin with SK can only be assessed in a larger trial with adequate statistical power.

### 10.1.2.6 The TETAMI (Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction) Study

*The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin (UFH) and of tirofiban versus placebo in the treatment of acute myocardial infarction (MI) for patients not thrombolysed: an international, randomized, double-blind, placebo controlled, factorial design study*

This was a multinational, randomized, double-blind, double-dummy, active/placebo-controlled, parallel group, 2 x 2 factorial study at 91 centers in 14 countries (5 sites in the US), with a 30-day study period for the primary analysis and a 6-month follow-up period for later analysis.

The study enrolled 1224 male or non-pregnant female  $\geq 18$  years old (21 years old for Argentina) with duration of ischemic symptoms  $\geq 30$  minutes within the previous 24 hours accompanied with sustained ST elevation  $> 0.2$  mV in  $\geq 2$  precordial leads or  $> 0.1$  mV in limb leads, or new left bundle branch block (LBBB [+ marker of necrosis]), or new Q-wave (+ marker of necrosis), and considered by attending physician as not eligible for thrombolytic use or primary PTCA/stent placement, and with signed informed consent.

The efficacy objective of this study was to demonstrate that enoxaparin given for 2-8 days to patients with acute MI not receiving thrombolytics, nor undergoing primary percutaneous transluminal coronary angioplasty (PTCA) significantly reduces the primary efficacy composite endpoint of death, reinfarction and recurrent angina by 30 days compared to UFH, and to assess the effects on 30-day triple endpoint of tirofiban versus placebo.

The safety objective was to demonstrate that enoxaparin was at least as safe as UFH based on the incidence of major hemorrhages; and to assess the safety of tirofiban and of the enoxaparin-tirofiban association.

There were four treatment groups (1224 patients):

- Enoxaparin/placebo (299 patients): enoxaparin, 30 mg intravenous (IV) bolus, followed by 1 mg/kg subcutaneously (SC) every 12 hours (h).
- Enoxaparin/tirofiban (305 patients): enoxaparin, 30 mg IV bolus, followed by 1 mg/kg SC every 12 h, plus tirofiban, 10  $\mu\text{g}/\text{kg}$  IV bolus, followed by continuous infusion (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ).
- UFH/placebo (306 patients): UFH, 70 U/kg IV bolus, followed by continuous infusion (15 U/kg/h initially) adjusted to activated partial thromboplastin time (aPTT).
- UFH/tirofiban (314 patients): UFH, 70 U/kg IV bolus, followed by continuous infusion (15 U/kg/h initially) adjusted to aPTT, plus tirofiban, 10  $\mu\text{g}/\text{kg}$  IV bolus, followed by continuous infusion (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ).

The study factorial 2 x 2 design and disposition of patients are shown in Figure 25.

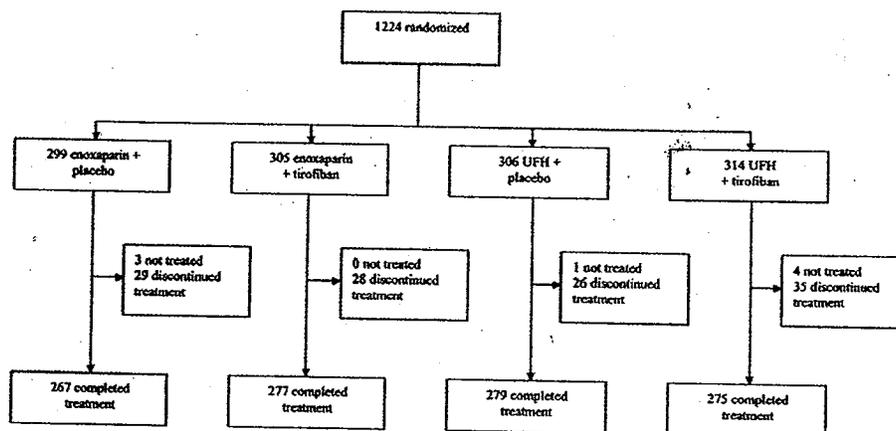


Figure 25 Study design and disposition of patients in the TETAMI study

The duration of treatment with UFH/enoxaparin was at least 2 days and up to 8 days. Tirofiban/placebo was administered between 2 days and 96 h (108 h if PTCA or stent replacement was performed between 84-96 h after acute MI). Aspirin was the concomitant therapy. All patients received a minimum of 160 mg aspirin on the first day of treatment and were treated with 100-325 mg oral aspirin given once daily for a minimum 30 days post-randomization.

**Efficacy Findings:** The incidence of the pooled primary efficacy endpoint (Table 67) was 15.7% enoxaparin vs 17.3% for UFH (odds ratio 0.89 [95% confidence interval {CI} = 0.66 to 1.21]) and 16.6% for tirofiban vs 16.4% for placebo (odds ratio 1.02 [95% CI 0.75 to 1.38]).

Table 67 Efficacy endpoints at 30 days for pooled enoxaparin and UFH groups in TETAMI study

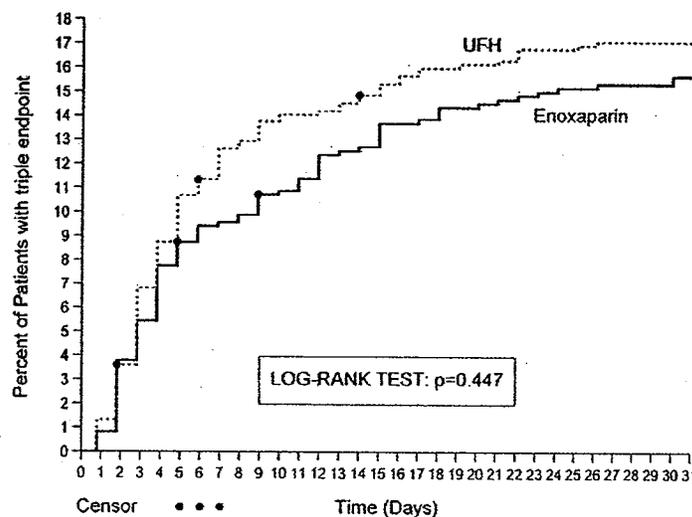
	All Patients (N = 1,224)	Enoxaparin (n = 604)	UFH (n = 620)	Odds Ratio (95% CI)
Primary efficacy outcome (triple end point)	202 (16.5%)	95 (15.7%)	107 (17.3%)	0.89 (0.66-1.21)
Secondary efficacy outcome (double end point)	105 (8.6%)	52 (8.6%)	53 (8.5%)	1.01 (0.68-1.50)
Any death	83 (6.8%)	42 (7.0%)	41 (6.6%)	
Any MI	33 (2.7%)	15 (2.5%)	18 (2.9%)	
Any recurrent angina	108 (8.8%)	49 (8.1%)	59 (9.5%)	
At least one revascularization	344 (28.1%)	157 (26.0%)	187 (30.2%)	
At least one PCI	264 (21.6%)	116 (19.2%)	148 (23.4%)	
At least one PCI on treatment	27 (2.2%)	12 (2.0%)	15 (2.4%)	
At least one CABG	81 (6.6%)	41 (6.8%)	40 (6.5%)	

No statistically significant treatment interactions were seen across the four individual treatment groups (P=0.846, Table 68), and survival rates were similar across all four treatment groups.

**Table 68 Efficacy endpoints at 30 days for enoxaparin and UFH groups in TETAMI study**

	All Patients (N = 1,224)	Enoxaparin/Placebo (n = 299)	Enoxaparin/Tirofiban (n = 305)	UFH/Placebo (n = 306)	UFH/Tirofiban (n = 314)	p Value for Treatment Interaction
Primary efficacy outcome (triple end point)	202 (16.5%)	46 (15.4%)	49 (16.1%)	53 (17.3%)	54 (17.2%)	0.846
Secondary efficacy outcome (double end point)	105 (8.6%)	26 (8.7%)	26 (8.5%)	28 (9.2%)	25 (8.0%)	
Any death	83 (6.8%)	22 (7.4%)	20 (6.6%)	23 (7.5%)	18 (5.7%)	
Any MI	33 (2.7%)	5 (1.7%)	10 (3.3%)	8 (2.6%)	10 (3.2%)	
Any recurrent angina	108 (8.8%)	22 (7.4%)	27 (8.9%)	27 (8.8%)	32 (10.2%)	

Figure 26 shows the time to first event for the composite triple endpoint in the pooled enoxaparin and UFH groups. Although the Kaplan-Meier curves separate by day 5, the differences between the groups did not reach statistical significance (p=0.447).



**Figure 26 Time to first event (death or adjudicated MI or adjudicated recurrent angina) at 30 days (enoxaparin vs. unfractionated heparin [UFH]) (ITT population, N = 1,224).**  
 Censor: marks point at which patients were withdrawn from study without further 30-day follow-up data.

**Safety Findings:** The TIMI major hemorrhage rate was 1.5% for enoxaparin versus 1.3% for UFH (odds ratio 1.16 [95% CI 0.44 to 3.02]) and 1.8% versus 1% for tirofiban versus placebo (odds ratio 1.82 [95% CI 0.67 to 4.95]).

**Table 69 Hemorrhage rates at 30 days in TETAMI study (all treated population, N = 1,216)**

	All Patients (N = 1,216)	Enoxaparin/Placebo (n = 297)	Enoxaparin/Tirofiban (n = 303)	UFH/Placebo (n = 306)	UFH/Tirofiban (n = 310)
TIMI major hemorrhage	17 (1.4%)	3 (1.0%)	6 (2.0%)	3 (1.0%)	5 (1.6%)
TIMI minor hemorrhage	51 (4.2%)	12 (4.0%)	12 (4.0%)	8 (2.6%)	19 (6.1%)
TIMI "loss no site"	39 (3.2%)	11 (3.7%)	14 (4.6%)	6 (2.0%)	8 (2.6%)
Any hemorrhage	194 (16.0%)	46 (15.5%)	61 (20.1%)	32 (10.5%)	55 (17.7%)

The results for the four individual treatment groups are shown in Table 69. The incidence of any hemorrhage was significantly higher in the pooled tirofiban vs placebo groups (18.9% [116 patients] in tirofiban group vs 12.9% [78 patients] in placebo group, p value = 0.005), with the highest incidence seen in the enoxaparin/tirofiban group (20.1%), Table 69. Eight patients suffered a stroke by the 30-day assessment (4 in the enoxaparin groups and 4 in the UFH groups).

**Clinical Review**

Khin Maung U

NDA 22-138

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The most common "non-hemorrhagic" AE was heart failure (7.0%), followed by chest pain (5.4%) and hypotension (4.8%). A total of 14.7% of patients had a serious adverse event (15.7% in pooled enoxaparin groups and 13.8% in pooled UFH groups).

Conclusions: This study did not show that enoxaparin significantly reduced the 30-day incidence of death, reinfarction, and recurrent angina compared with UFH in *non-reperfused* STEMI patients. However, enoxaparin appears to have a similar safety and efficacy profile to UFH. Additional therapy with tirofiban did not appear beneficial.

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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**Clinical Review**

Khin Maung U

NDA 22-138

Lovenox® (Enoxaparin sodium - solution for injection)

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Khin U

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MEDICAL OFFICER

Enoxaparin vs heparin in STEMI patients produces net clinical benefit (fewer deaths, myocardial re-infarctions & episodes of urgent revascularization at 30 days) at a cost of increased major bleeds but no increased intracranial bleeds. Recommend approval.