

6.2.1.13.2 Comments on Specific Safety Parameters (cont)

Transfusions in the PRISM-PLUS trial

More subjects in the combination group (4.0%) than in the heparin group (2.8%) required a transfusion, although this difference was not statistically significant ( $p=0.21$ ). Twenty-seven (3.5%) subjects in the combination group and 18 (2.3%) subjects in the heparin group received transfusions of packed red blood cells ( $p=0.17$ ). Five (0.6%) of the subjects in the combination group received platelet transfusions compared to 4 (0.5%) of the subjects in the heparin group ( $p=0.75$ ). In the subjects who did receive platelet transfusions, there were no differences in the number of transfused units between the two treatment groups.

Tat 6.2.1.13.2.7 Subjects requiring transfusion in the PRISM-PLUS trial<sup>a</sup>.

	Tirofiban (N=345)	Comb. (N=773)	Heparin (N=797)	p value T+H vs. H
<b>Type</b>	n (%)	n (%)	n (%)	
<b>Any Transfusion</b>				0.21
No	327 (94.8%)	742 (96.0%)	775 (97.2%)	
Yes	18 (5.2%)	31 (4.0%)	22 (2.8%)	
<b>Whole Blood</b>				0.72
No	343 (99.4%)	769 (99.5%)	794 (99.6%)	
Yes	2 (0.6%)	4 (0.5%)	3 (0.4%)	
<b>FFP</b>				0.79
No	339 (98.3%)	766 (99.1%)	791 (99.2%)	
Yes	6 (1.7%)	7 (0.9%)	6 (0.8%)	
<b>PRBC</b>				0.17
No	328 (95.1%)	746 (96.5%)	779 (97.7%)	
Yes	17 (4.9%)	27 (3.5%)	18 (2.3%)	
<b>Cryoprecipitates</b>				0.99
No	345 (100%)	772 (99.9%)	796 (99.9%)	
Yes	0 (0.0%)	1 (0.1%)	1 (0.1%)	
<b>Platelets</b>				0.75
No	342 (99.1%)	768 (99.4%)	793 (99.5%)	
Yes	3 (0.9%)	5 (0.6%)	4 (0.5%)	
<b>Other</b>				0.68
No	345 (100%)	770 (99.6%)	795 (99.7%)	
Yes	0 (0.0%)	3 (0.4%)	2 (0.3%)	

a. Data from SPONSOR at request of medical reviewer.

### 6.2.1.13.2 Comments on Specific Safety Parameters (cont)

#### Transfusions in the PRISM-PLUS trial (cont)

Table 6.2.1.13.2.8 Number of PRBC units transfused in the PRISM-PLUS trial<sup>a</sup>.

	<b>Tirofiban (N=345)</b>	<b>Comb. (N=773)</b>	<b>Heparin (N=797)</b>	<b>p value T+H vs. H</b>
<b>Type and Number of Units</b>	n (%)	n (%)	n (%)	
<b>Whole Blood</b>				
0	343 (99.4%)	<b>769 (99.5%)</b>	794 (99.6%)	
1	1 (0.3%)	2 (0.3%)	1 (0.1%)	
2	1 (0.3%)	1 (0.1%)	2 (0.2%)	
4	0 (0.0%)	1 (0.1%)	0 (0.0%)	
<b>Mean (+S.D.)</b>	<b>.009 (.120)</b>	<b>.010 (0.169)</b>	<b>.006 (.106)</b>	<b>0.87</b>
<b>FFP</b>				
0	339 (98.3%)	766 (99.1%)	791 (99.2%)	
1	1 (0.3%)	0 (0.0%)	1 (0.1%)	
2	2 (0.6%)	2 (0.3%)	3 (0.4%)	
3	0 (0.0%)	1 (0.1%)	0 (0.0%)	
4 or more	3 (0.8%)	4 (0.5%)	2 (0.3%)	
<b>Mean (+S.D.)</b>	<b>.052 (.435)</b>	<b>.045 (.575)</b>	<b>.020 (.260)</b>	<b>0.29</b>
<b>PRBC</b>				
0	328 (95.1%)	746 (96.5%)	779 (97.7%)	
1	0 (0.0%)	5 (0.6%)	3 (0.4%)	
2	8 (2.3%)	14 (1.8%)	7 (0.9%)	
3	0 (0.0%)	1 (0.1%)	2 (0.2%)	
4 or more	9 (2.6%)	7 (1.0%)	6 (0.8%)	
<b>Mean (+S.D.)</b>	<b>.194 (.988)</b>	<b>.106 (.732)</b>	<b>.077 (.628)</b>	<b>0.054</b>
<b>Platelets</b>				
0	342 (99.1%)	768 (99.4%)	<b>793 (99.5%)</b>	
1	<b>0 (0.0%)</b>	0 (0.0%)	<b>1 (0.1%)</b>	
6	<b>1 (0.3%)</b>	0 (0.0%)	<b>0 (0.0%)</b>	
<b>8</b>	<b>0 (0.0%)</b>	3 (0.4%)	1 (0.1%)	
9 or more	2 (0.6%)	2 (0.2%)	2 (0.3%)	
<b>Mean (+S.D.)</b>	<b>.128 (1.48)</b>	<b>.067 (.873)</b>	<b>.035 (.555)</b>	<b>0.76</b>

a. Data from sponsor at request of medical reviewer.

#### Thrombocytopenia

Low absolute platelet counts were more common in the tirofiban +heparin group than in the heparin group, regardless of the level used to detect thrombocytopenia.

Table 6.2.1.13.2.9 Incidence of decreased platelet counts in PRISM-PLUS<sup>a</sup>.

<b>Lab adverse event</b>	<b>Tirofiban alone n=345</b>	<b>Tirofiban + Heparin n=773</b>	<b>Heparin alone n=797</b>	<b>p value T+H vs. H<sup>b</sup></b>
<b>Platelet count decrease to &lt;100,000/mm<sup>3</sup></b>	<b>7 (2.1%)</b>	<b>19 (2.5%)</b>	<b>9 (1.2%)</b>	<b>0.056</b>
<b>Platelet count decrease to &lt;90,000/mm<sup>3</sup></b>	6 (1.8%)	14 (1.9%)	6 (0.8%)	0.073
<b>Platelet count decrease to &lt;50,000/mm<sup>3</sup></b>	<b>1 (0.3%)</b>	4 (0.5%)	2 (0.3%)	0.44
<b>Platelet count decrease to &lt;20,000/mm<sup>3</sup></b>	<b>0 (0%)</b>	1 (0.1%)	0 (0%)	0.99

a. Data from NDA volume 1.42, ref. 5, page 2714 and appendix 4.1.29.

b. p value per the sponsor.

Serious bleeding complications as a result of thrombocytopenia occurred in 2 subjects in the tirofiban alone group, 1 subject in the combination group, and 2 subjects in the heparin alone group. The clinical consequences of thrombocytopenia will be discussed further in sections 8.1 and 8.2.

#### 6.2.1.14 PRISM-PLUS Efficacy Summary

The three groups of subjects in the PRISM-PLUS trial were well-balanced as regards demographics and clinical presentation at time of entry into the trial (see tables 6.2.1.12.1.1 to 6.2.1.12.1.3, p. 80-81). With few exceptions, the groups were also well-balanced with regard to concomitant medications used during the trial. When compared with the heparin group, subjects in the tirofiban +heparin group were more likely to be using calcium channel blockers (49% vs. 43%,  $p=0.020$ ) and ACE inhibitors (9.6% vs. 6.3%,  $p=0.020$ ). The groups were also well-balanced with regard to duration of study drug therapy (see section 6.2.1.12.2c, p. 83).

1. In the PRISM-PLUS trial, use of tirofiban + heparin was associated with a significant decrease in the incidence of refractory cardiac ischemia, new myocardial infarction, or death within 7 days of start of study drug (the pre-specified primary endpoint). In the combination group, 100/773 subjects met the primary endpoint (12.9%) versus 143/797 in the heparin group (17.9%,  $p=0.004$ ). In the tirofiban alone arm, which was discontinued early due to safety concerns, 59/345 (17.1%) met the primary endpoint, an incidence rate which was not different from the heparin group. The incidence of the composite endpoint was also significantly reduced in the tirofiban +heparin group at days 30 and 180 when compared with heparin alone (table 6.2.1.12.2d.1, p. 85). Of the components of the endpoint, the incidence of refractory ischemic conditions (RIC) and MIs (both fatal and non-fatal) were also significantly reduced in the combination group at 7 and 30 days. No significant difference in the incidence of death was detected between the tirofiban +heparin and heparin-alone groups. These results persisted in the 'per-protocol' analysis of the primary endpoint and its components (table 6.2.1.12.3.2, p. 87).

2. The sponsor performed a series of post-hoc and secondary analyses aimed at defining the effect of tirofiban in this population of subjects with UAP/NQWMI. First, the sponsor analyzed the incidence of readmission for UAP, and for the combination of MI/Death (see table 6.2.1.12.3.3, p. 88). Subjects in the tirofiban +heparin group had a lower incidence of MI/Death at the time points measured, but no difference in the rate of readmission for UAP was seen.

3. Next, the sponsor analyzed the effect of tirofiban on angiographically apparent thrombus, measured within 96 hours of drug administration (see tables 6.2.1.12.3.8 to 6.2.1.12.3.9, p. 91). Depending on the measurement used, there was an effect of tirofiban +heparin to reduce the amount of angiographically-apparent thrombus.

4. Next, the sponsor analyzed the receipt of invasive cardiac procedures in the three groups (see table 6.2.1.12.3.10, p. 92). All three treatment groups had similar incidence of procedures during the initial hospitalization. No trend towards fewer procedures was detected in the tirofiban +heparin group.

5. Next, the sponsor noted that subjects who experienced RIC after entering the trial were at high risk of requiring further cardiac procedures (see table 6.2.1.12.3.11). For instance, 67-91% of these subjects had a PTCA, 30-50% had a CABG, and 8.7-14.9% had a stent placement. The sponsor analyzed the subjects who developed RIC within 48 hours of starting the study, a who made up only 5.6% of the total subjects (107/1915). In this group, there were fewer revascularization procedures of any kind, and fewer CABGs in the combination group. The incidence of MIs in the combination population was also decreased (1/47 (23.5%) in heparin alone group, 5/37 (13.5%) in the tirofiban +heparin group).

Next, the sponsor analyzed the subsequent cardiac events in the subjects who developed RIC within 7 days of starting the study, a slightly larger population (2120/1915, 11.1%), see table 6.2.1.12.3.11, p. 92. The trend towards fewer MIs and cardiac procedures persisted.

6. The sponsor also examined the incidence of two variations of the composite endpoint: 'Composite/procedures,' and 'Composite/revascularization' (see table 6.2.1.12.3.13, p. 93). For both endpoints, the tirofiban +heparin group had a lower incidence of events at 48 hours and 7 days, compared with heparin alone.

7. The sponsor also analyzed the clinical outcomes for the subjects in the trial who underwent a PTCA (a population somewhat analogous to the RESTORE trial). Approximately 30% of each treatment group underwent PTCA during their initial hospitalization in the PRISM-PLUS trial. The tirofiban +heparin group had a lower incidence of the combined primary endpoint, fatal and nonfatal MIs, and the composite MI/death endpoint during the first 7 and 30 days after PTCA than did either heparin or tirofiban alone (see table 6.2.1.12.3.14, p. 94). This effect was nominally significant at the end of the 7 day follow-up. The group that did not receive PTCA was also analyzed. In this group, the tirofiban +heparin had a lower incidence of the primary endpoint (see table 6.2.1.12.3.14, p. 94).

The sponsor also analyzed the incidence of the primary endpoint in subjects who received PTCA while on study drug. Subjects in the tirofiban +heparin group had a lower overall incidence of the primary endpoint when compared with the heparin group (see table 6.2.1.12.3.16, p. 95). These issues are discussed further in the integrated efficacy summary, section 7.0.

5. The sponsor also performed a series of pre-specified sub-group analyses (see table 6.2.1.12.3.18, p. 96). Overall, subjects receiving tirofiban +heparin had a lower incidence rate of the primary endpoint (death, MI, RIC) than the subjects in the heparin group for all evaluated subgroups. Some subgroups (i.e., older subjects, subjects taking calcium channel blockers before study entry, and subjects presenting with ST-segment depression) had a higher incidence of clinical events, regardless of the study group.

### 6.2.1.15 PRISM-PLUS Safety Summary

The safety profile of tirofiban will be examined in greater detail in the integrated safety summary (sections 8.0 to 8.2). The following comments relate to the data presented above.

1. Death occurred at a similar, low rate in both tirofiban +heparin and heparin groups. There was a significant increase in the % of deaths in the tirofiban alone arm at the end of 7 days, which led to the discontinuation of that arm of the study. The relatively small number of events used to make this decision are presented in section 6.2.1.12.3 above (tables 6.2.3.12.3.4 to 6.2.12.3.7, p. 89). This issue is discussed further in the safety summary. While some of the deaths in the tirofiban +heparin and heparin arms were associated with clinical bleeding, none could be clearly related to tirofiban administration.

2. The tirofiban +heparin group had more AEs thought to be drug-related by the investigators than the heparin group, more serious and drug-related AEs, more discontinuations of all types due to AEs, and more discontinuations for bleeding AEs, when compared with the heparin alone group (see table 6.2.1.13.1 and 6.2.1.13.2.2, p. 97). This excess bleeding was seen with IV sites, catheterization sites, nosebleeds, GU/hematuria and 'other' bleeding sites (see table 6.2.1.13.2.6, p. 99). There were no retroperitoneal or intracranial bleeds in the combination group. There was no difference between the heparin and combination groups in the incidence of life-threatening bleeds.

3. Thrombocytopenia occurred at a higher incidence rate in the tirofiban +heparin group than in the heparin group (2.5% vs. 1.2%,  $p=0.056$ , see table 6.2.1.13.2.9, p. 102).

4. Subjects in the tirofiban +heparin group required PRBC transfusion at a higher rate than subjects in the heparin group (3.1% vs. 2.3%,  $p=0.17$ , see tables 6.2.1.13.2.7 and 6.2.1.13.2.8, p. 101).

5. No unexpected toxicities of tirofiban were identified by this reviewer from the PRISM-PLUS database.

## 6.2.2 Review of the **PRISM Trial**

### 6.2.2.1 Title of Study

A randomized, parallel, double-blind study to investigate the safety and clinical efficacy of MK-0383 versus heparin in subjects with unstable angina/non-Q-wave myocardial infarction (PRISM).

### 6.2.2.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 1.37, Table A- 1 (pages A-6 to A- 10 1).

PRISM was a multicenter investigation, with 56 investigators in the U.S. and 72 investigators internationally.

### 6.2.2.3 Background

The sponsor points out that the trials exploring the effect of Reopro on the UAP/ NQWMI population have been in subjects undergoing PTCA (see section 2.2, p. 13 and Appendix Seven, p. 358). The current trial was designed to assess the efficacy and safety of tirofiban in the setting of unstable angina pectoris/ non-Q-wave MI (UAPMQWMI), independent of whether the subjects were scheduled to receive angiography or other cardiac interventions (PTCA, stent placement, atherectomy). The sponsor argues that this trial will give valuable information regarding the placed of tirofiban in a setting apart from the post-PTCA subject.

Additionally, the other phase III trials of tirofiban (PRISM-PLUS, RESTORE) used it in combination with heparin. The potential role for tirofiban alone, without the concomitant use of heparin, was explored in this trial.

#### Initial protocol

The original U.S. protocol, submitted 12.31.93, underwent two revisions during the course of the 3-year study.

The first U.S. protocol amendment was submitted on 8.4.94 (prior to the first safety analysis):

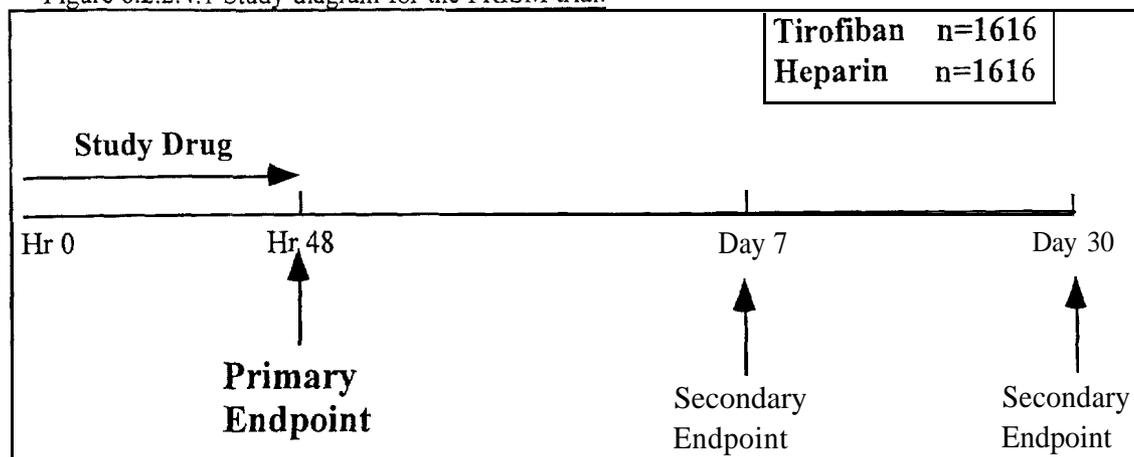
1. Revised the criteria for inclusion and exclusion section of the original protocol;
2. Revised the protocol's drug supplies, from 'open label' to double-blind;
3. Revised the clinical and laboratory measurements for the safety and efficacy sections;
4. Revised the definition for discontinuation due to thrombocytopenia;
5. Revised the definitions for ischemic episodes, refractory ischemia, and myocardial infarction were revised.
6. Addition of two objectives regarding tirofiban clearance (effect of concomitant medications and confirmation of lack of effect of age and gender);
7. Revision of following sections: (1) study design and treatment, (2) data analysis, and (3) adverse experiences.

The second U.S. protocol amendment was submitted 1.24.96 (after first safety analysis):

1. Documented the Steering Committee's decision to expand the sample size from the original 2000 subjects to 3 100 subjects based on results from an interim analysis;
2. Revised the following sections: (1) criteria for inclusion and exclusion, (2) study design and treatment, (3) clinical and laboratory measurements for safety and efficacy, and (4) data analysis.
3. Addition of women of childbearing potential with a negative pregnancy test within 12 hours prior to randomization to the eligible pool;
4. Addition of subjects with chest pain who only had entry evidence of elevated CK enzymes and/or MB fraction consistent with a NQWMI;
5. The collection of plasma samples was discontinued, and the definitions of clinical efficacy were revised.

#### 6.2.2.4 Study Design

Figure 6.2.2.4.1 Study diagram for the PRISM trial.



#### General

This was a multicenter, randomized, parallel, double-blind study comparing the clinical efficacy of tirofiban to heparin in subjects with unstable angina or non-Q-wave myocardial infarction. Subjects with anginal chest pain within the previous 24 hours, and a documented history of coronary artery disease, those presenting with ECG evidence of myocardial ischemia, and those with chest pain and evidence of elevated CPK-MB fractions consistent with NQWMI were eligible for the trial. Subjects were randomly assigned to receive either tirofiban or heparin for 48 hours, and then monitored during the initial hospitalization and until 30 days after start of infusion for clinical endpoints and adverse events. During the 48-hour infusion period, catheterization was not performed unless the endpoint of refractory ischemia or myocardial infarction had been met (defined below).

All nonsteroidal anti-inflammatory agents, and other antiplatelet or anticoagulant drugs, including warfarin and ticlopidine, were to be discontinued at the time the study commenced and were withheld until completion of the infusion. Other medications were prescribed at the discretion of the physician (e.g., nitrates, b-blockers and calcium antagonists). If the subject had been receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent and dosage could be continued; any change in dosage after randomization was monitored and noted. All subjects, regardless of prior aspirin use, received 300 to 325 mg of aspirin within 24 hours before study drug initiation, unless contraindicated.

The clinical events which were followed included: refractory ischemia; progression to new myocardial infarction; or death. Their definitions appear below. Laboratory evaluations, electrocardiographic monitoring, and physical examinations were performed at baseline and periodically during the infusion period. All adverse clinical or laboratory events were recorded. The subjects were also closely monitored for evidence of bleeding during the study.

#### Definitions of clinical events

##### **Refractory ischemia (RI)**

During the initial hospitalization RIC was defined as any of the following clinical events:

a) Refractory Ischemia - defined as anginal chest pain with ischemic ST-T changes (new ST-segment depression or elevation of 2.0 mV or T-wave inversion in two contiguous ECG leads). This pain could occur either as a single episode persisting for  $\geq 20$  minutes, or  $\geq 2$  episodes persisting for  $\geq 10$  minutes each within a 1-hour period, despite full medical therapy (including, at least, an infusion of nitroglycerin plus use of a  $\beta$ -blocker or calcium channel blocker titrated to heart rate and blood pressure).

b) Hemodynamic Instability - defined as clinical evidence of pulmonary edema, (new rales over 1/3 lung fields, tachypnea, evidence of hypoxemia) or hypotension (systolic blood pressure  $< 95$  mmHg, not related to antianginal therapy; need for fluid volume or pressor therapy) in the setting of recurrent angina or ischemic electrocardiogram changes.

##### **Revascularizations**

Coronary angioplasty, atherectomy, stent placement, or CABG was recorded. The indication for each procedure, and whether the procedure was performed for recurrent pain or compelling anatomic indications (i.e.,  $> 90\%$  stenosis of proximal LAD or right coronary artery).

#### 6.2.2.4 Study Design (cont)

##### Ischemic episodes

All subject-reported episodes of angina during hospitalization were recorded during the initial hospitalization, along with time and duration of episode. Any non-routine ECGs were also recorded and any ischemic changes noted.

##### Myocardial infarction

Additional creatine kinase measurements were obtained after an episode of typical ischemic chest pain lasting 10 minutes or more and were repeated 6 to 8 hours later. Once this 'rule out MI' cycle of CPK drawing had begun, it was not necessary to draw blood for CPKs with every episode of chest pain. However, CPKs were to be drawn on a 6- to 8-hour interval for 24 hours or until the episodes of chest pain had subsided. The development of an MI after randomization was defined as typical chest pain with new ST-T changes and/or new pathologic Q-waves ( $>0.03$  sec in duration), accompanied by a rise in serum creatine kinase to  $>2$  times the upper limit of normal, with serum CK-MB (if available)  $>5\%$  of total CK. The Steering Committee further defined MIs associated with invasive interventions as follows: following PTCA, atherectomy, or stent, a new MI will require the presence of creatine kinase  $\geq 3$  times the upper limit of normal within 24 to 36 hours of the PTCA. Following CABG, criteria for a new MI will be the development of Q-waves on the electrocardiogram within 48 to 72 hours of the start of the surgery.

In subjects enrolled with a non-Q-wave myocardial infarction, a new myocardial infarction was defined as a rise in creatine kinase to  $\geq 50\%$  above the preceding sample and which was at least  $\geq 2$  times the upper limit of normal and not associated with the original event, but the subject must have had new recurrent angina and had ECG changes consistent with ischemia.

##### Death

Death (regardless of etiology) occurring during the 6 months after the initiation of study drug was recorded.

#### 6.2.2.5 Primary and Secondary Endpoints

##### Primary endpoint (combined endpoint)

1. The incidence of refractory ischemia (RI), new myocardial infarction or death at 48 hours of study drug infusion.

##### Secondary endpoints

1. The incidence of the refractory cardiac ischemia, new myocardial infarction or death through 7 days after start of study drug infusion.

2. The incidence of the refractory cardiac ischemia, new myocardial infarction or death through 30 days after start of study drug infusion.

#### 6.2.2.6 Number of subjects/ randomization

Assuming a 14.3% event rate in the heparin group and a 30% reduction in events (10% event rate) in the tirofiban group, a sample size of 1000 subjects per treatment group had an 80% power to detect a difference between tirofiban and heparin (5% significance level, 2-sided test). However, based on a lower than expected blinded pooled event rate ( $<6\%$  during the entire trial), the Steering Committee recommended an increase in the sample size to a total enrollment of 3100 subjects (see statistical considerations). Ultimately, 3232 subjects were enrolled. Subjects were randomly assigned, via a computer-generated allocation schedule, to receive either tirofiban or heparin.

Table 6.2.2.6.1 Patients enrolled in the PFUSM trial.

Tirofiban n=1616	Heparin n=1616
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### 6.2.2.7 Inclusion/ Exclusion Criteria

#### Inclusion Criteria for PRISM

The study population consisted of subjects who presented to hospital with myocardial ischemic pain caused either by unstable angina (UAP) or non-Q-wave MI (NQWMI), defined as one of the following:

1. Accelerated pattern of anginal pain (episodes of angina that were more frequent, severe, longer in duration, and/or precipitated by less exertion) with ECG evidence of myocardial ischemia.
2. Anginal pain at rest or with minimal effort.
3. Subjects must:
  - a) have had their most recent pain within 24 hours of initiation of study drug;
  - b) have clinical evidence of underlying coronary artery disease by having one of the following:
    - 1) New or persistent or transient ST-segment depression  $\geq 0.1$  mV (0.08 seconds after the J-point) in at least two contiguous leads;
    - 2) New or transient ( $< 20$  minutes) ST-segment elevation  $\geq 0.1$  mV (0.08 seconds after the J-point) in at least two contiguous leads; or
    - 3) New persistent or transient T-wave inversion in two contiguous leads.
4. Be 218 years of age.

#### Exclusion Criteria for PRISM

- 1) Women of childbearing potential were excluded unless they had a negative pregnancy test obtained within 12 hours prior to randomization and there was no reason to suspect early pregnancy.
- 2) Presence of new pathologic Q-waves ( $> 0.03$  seconds in duration) or ST-segment elevation  $\geq 0.1$  mV in two contiguous leads persisting for  $\geq 20$  minutes, suggestive of evolving acute Q-wave myocardial infarction.
- 3) Angina precipitated by obvious provoking factors (e.g., arrhythmia, severe anemia, hypotension, or hyperthyroidism).
- 4) Coronary angioplasty within 6 months or coronary artery bypass surgery within 1 month.
- 5) History or symptoms (e.g., pain radiating to the back) suggestive of aortic dissection.
- 6) Patients with uncontrolled severe (resulting in hemodynamic instability) cardiac arrhythmias, including persistent sinus tachycardia.
- 7) Heparin allergy or intolerance (including heparin-induced thrombocytopenia).
- 8) Thrombolytic therapy within 48 hours prior to enrollment, or documented MI within 48 hours of most recent episode of chest pain.
- 9) Contraindications to anticoagulation:
  - a) Recent ( $< 1$  year) or active present bleeding disorder including a history of gastrointestinal bleeding, hematuria, or presence of occult blood in the stool. Any subject with a known coagulopathy, platelet disorder, or history of thrombocytopenia was also excluded.
  - b) Any confirmed persistent recording of systolic blood pressure exceeding 180 mmHg and/or diastolic blood pressure exceeding 110 mmHg at time of enrollment.
  - c) Any history of hemorrhagic cerebrovascular disease or active intracranial pathologic process. Any history of cerebrovascular disease (or transient ischemic attack) within 1 year.
  - d) Traumatic or prolonged cardiopulmonary resuscitation within the 2 weeks prior to study enrollment.
  - e) Severe trauma within 3 months prior to study enrollment.
  - f) Major surgical procedure within 1 month prior to study enrollment.
  - g) Active peptic ulcer disease within 3 months prior to study enrollment.
  - h) Invasive procedure (or lithotripsy) within 14 days of enrollment that would have significantly increased the risk of hemorrhage (such as organ biopsy). (Note that subjects who had undergone recent coronary catheterization could be enrolled 24 hours after groin hemostasis was achieved.)
  - i) Probable pericarditis.
  - j) Presence of known significant retinopathy (i.e., hemorrhages, exudates, or neovascularization).
- 10) Inability to interpret ST-T segment changes on ECG (e.g., complete left bundle branch block and paced rhythm).
- 11) Patients with acute pulmonary edema (rales present over more than 50% of the lung fields) or subjects with severe congestive heart failure (New York Heart Association Functional Class III or IV). Patients with cardiogenic shock were also excluded.
- 12) Patients with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.

#### 6.2.2.4 Study Design

##### Exclusion Criteria for PRISM (cont)

13) Patients with clinically important systemic renal, pulmonary, hepatic, endocrine (e.g., uncontrolled diabetes or uncontrolled thyroid disease), neurological, or hematological disorders.

14) Patients with clinically important abnormal laboratory findings including:

- a) Serum creatinine >2.5 mg/dL (>220 µmol/L);
- b) Hemoglobin <11 g/dL (<110 g/L) or hematocrit <34%;
- c) Platelet count <150,000/mm<sup>3</sup> (<150 X 10<sup>9</sup> /L);
- d) Prothrombin time >1.3 X control (International Normalized Ratio (INR) > 1.5).

15) Patients receiving another investigational drug within 4 weeks prior to the study (including ANY prior exposure to tirofiban).

16) Patients with any other medical condition, which, in the investigator's opinion, made survival for the duration of the study unlikely, or would otherwise interfere with optimal participation in the study or produce a significant risk to the subject.

17) Inability to give informed consent.

#### 6.2.2.8 Dosage/ Administration

The three phase III trials submitted in the NDA utilized three separate dosing regimens for tirofiban, as seen in the table below.

Table 6.2.2.8.1 Dosing regimens used in the phase III tirofiban studies.

Trial	Design (arms)	Tirofiban Regimen	Heparin Regimen
PRISM	1. Tirofiban 2. Heparin	0.6 µg/kg/min loading dose (30 mins.) 0.15 µg/kg/min maintenance	5000 U bolus 1000 U/hr infusion with adjustment as needed
PRISM-PLUS	1. Tirofiban  2. Tirofiban +Heparin 3. Heparin	0.6 µg/kg/min loading dose (30 mins.) 0.15 µg/kg/min maintenance  0.4 µg/kg/min loading dose (30 mins.) 0.10 µg/kg/min maintenance	None  5000 U bolus 1000 U/hr infusion with adjustment as needed
RESTORE	1. Tirofiban 2. Placebo	10 µg/kg loading dose (3 mins.) 0.15 µg/kg/min maintenance	10,000 U bolus (150 u/kg if subject <70 kg) No infusion after PTCA complete

The selection of tirofiban dosing regimen in the PRISM trial was based on experience in Phase II studies with tirofiban given with ASA, but not heparin, in subjects with UAP/MQWMI (protocols #004 and #005). These studies suggest that, at median inhibition of platelet aggregation >70%, the GP IIb/IIIa inhibitors could reduce adverse cardiac ischemic outcomes during the drug infusion compared to heparin. In particular, the Phase II experience with tirofiban suggested that a loading infusion of 0.6 µg/kg/min for 30 minutes followed by a maintenance regimen of 0.15 µg/kg/min could achieve consistent inhibition of platelet aggregation across a population of subjects with UAP/MQWMI. See appendix 8, section 20.0, for details of the dosing regimen chosen for each Phase III study.

The study drugs (tirofiban and heparin) were administered from two bags. Bag 1 contained either tirofiban or normal saline (NS) 'placebo' and Bag 2 contained either heparin or D5W. The syringe contained either heparin or normal (0.9%) saline (for the heparin bolus or its sham equivalent). The contents of the syringe were given as a bolus followed by intravenous infusion of Bags 1 and 2 simultaneously.

##### Tirofiban alone

Patients randomized to receive tirofiban received a loading dose of tirofiban at a rate of 0.6 µg/kg/min over 30 minutes. After 30 minutes, the infusion rate was adjusted downward to 0.15 µg/kg/min for the next 47.5 hours.

#### 6.2.2.8 Dosage/ Administration (cont)

##### Heparin alone

Patients randomized to receive heparin received a 5000 U intravenous bolus followed by a maintenance infusion of 1000 U per hour for 48 hours. At 6, 12, 24, and 48 hours (and as needed), the unblinded coinvestigator monitored the activated partial thromboplastin time (aPTT) and adjusted the heparin infusion to maintain the aPTT approximately 2X control by a standard nomogram. In subjects who received tirofiban, there were also adjustments of the Bag 2 placebo for heparin, in order to maintain the blind. All aPTT results remained blinded to individuals directly responsible for subject care, including those who reported adverse events.

##### Aspirin (ASA) administration

All subjects, regardless of prior aspirin (ASA) use, received 300 to 325 mg of ASA within 24 hours before initiation of study drug, and after 24 and 48 hours of the study drug infusion, unless contraindicated. Aspirin was continued daily, thereafter, for at least 30 days at a dose of 80 to 325 mg, unless contraindicated.

##### Anti-ischemic therapy

Medications other than antiplatelet and anticoagulant drugs could be prescribed during hospitalization at the discretion of the treating physician. Oral or sublingual nitrates were usually the first choice for additional anti-ischemic therapy. Intravenous nitroglycerin and/or a P-blocker was added as indicated. Calcium channel blockers could also be added if deemed necessary by the investigator. If the subject was receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent could be continued.

All nonsteroidal anti-inflammatory agents and nonstudy antiplatelet or anticoagulant drugs were discontinued at the time the study commenced and withheld until completion of the infusion. Warfarin or other anticoagulants, including open-label heparin (except IV flushes), were not to be instituted until completion of the study.

#### 6.2.2.9 Duration/ Adjustment of Therapy

Tirofiban or heparin was administered for 48 hours.

##### Discontinuation of therapy

Study drug administration was discontinued if any of the following occurred:

- 1) A decision to administer thrombolytic therapy.
- 2) A decision to proceed to emergent angiography or revascularization.
- 3) A decision to use intra-aortic balloon counter-pulsation,
- 4) If at any time during the study the investigator responsible for the clinical care of the subject decided that tirofiban or heparin therapy was contraindicated.
- 5) Clinically relevant bleeding (or a significant decrease 23.5 g/dl in hemoglobin levels from predrug values).
- 6) Significant thrombocytopenia (repeated/confirmed platelet count  $<90,000/\text{mm}^3$ ).

In the event the study drug was discontinued prematurely, all examinations which were to have taken place after 48 hours were performed (physical examination, 12-lead ECG, complete laboratory evaluation including PT and aPTT). Additionally, plasma samples were collected immediately prior to cessation of study drugs and 1 to 6 hours after cessation of study drugs. The subject was monitored for at least 24 hours after study drug had been discontinued, and if possible, post-termination tests were obtained 24 hours after cessation of study drugs.

8.1.3 Clinical adverse events (AEs) from the Phase II-III Tirofiban safety database (cont)

Table 8.1.3.1 Nonbleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912 (cont)<sup>a</sup>.

	Tirofiban + Heparin n=1953	Heparin/ Procedures n=1887	Tirofiban n=2032	Heparin/ No Procedures n=1659	Total Heparin <sup>b</sup> n=3546
<b>Digestive System</b>	470 (24.1%)	448 (23.7%)	270 (13.3%)	168 (10.1%)	616 (17.4%)
Acid regurgitation	26 (1.3%)	26 (1.4%)	11 (0.5%)	6 (0.4%)	32 (0.9%)
Constipation	103 (5.3%)	93 (4.9%)	85 (4.2%)	39 (2.4%)	132 (3.7%)
Diarrhea	28 (1.4%)	31 (1.6%)	20 (1.0%)	15 (0.9%)	46 (1.3%)
Dyspepsia	40 (2.0%)	41 (2.2%)	26 (1.3%)	22 (1.3%)	63 (1.8%)
Nausea	226 (11.6%)	238 (12.6%)	96 (4.7%)	72 (4.3%)	310 (8.7%)
Vomiting	106 (5.4%)	101 (5.4%)	42 (2.1%)	25 (1.5%)	126 (3.9%)
<b>Endocrine System</b>	6 (0.3%)	0 (0.0%)	4 (0.2%)	2 (0.1%)	2 (<0.1%)
<b>Hemic and Lymphatic System</b>	20 (1.0%)	12 (0.6%)	18 (0.9%)	6 (0.4%)	18 (0.5%)
<b>Metabolic/Nutritional/Immune Systems</b>	24 (1.2%)	31 (1.6%)	19 (0.9%)	9 (0.5%)	40 (1.1%)
<b>Musculoskeletal System</b>	554 (28.4%)	540 (28.6%)	145 (7.1%)	77 (4.6%)	617 (17.4%)
Pain, arm	35 (1.8%)	28 (1.5%)	7 (0.3%)	4 (0.2%)	32 (0.9%)
Pain, back	443 (22.7%)	425 (22.5%)	68 (3.3%)	35 (2.1%)	460 (13.0%)
Pain, leg	50 (2.6%)	32 (1.7%)	11 (0.5%)	8 (0.5%)	40 (1.1%)
Pain, shoulder	26 (1.3%)	34 (1.8%)	17 (0.8%)	9 (0.5%)	43 (1.2%)
<b>Nervous System and Psychiatric</b>	642 (32.9%)	645 (34.2%)	512 (25.2%)	353 (21.3%)	1007 (28.4%)
Agitation	30 (1.5%)	32 (1.7%)	12 (0.6%)	5 (0.3%)	37 (1.0%)
Anxiety	127 (6.5%)	148 (7.8%)	78 (3.8%)	48 (2.9%)	196 (5.5%)
Anxiety disorder	26 (1.3%)	21 (1.1%)	20 (1.0%)	2 (0.1%)	23 (0.6%)
Confusion	37 (1.9%)	37 (2.0%)	17 (0.8%)	14 (0.8%)	51 (1.4%)
Dizziness	52 (2.7%)	41 (2.2%)	41 (2.0%)	15 (0.9%)	56 (1.6%)
Headache	336 (17.2%)	367 (19.4%)	323 (15.9%)	237 (14.3%)	604 (17.0%)
Insomnia	130 (6.7%)	129 (6.8%)	95 (4.7%)	62 (3.7%)	191 (5.4%)
Nervousness	41 (2.1%)	32 (1.7%)	8 (0.4%)	5 (0.3%)	37 (1.0%)
Somnolence	21 (1.1%)	29 (1.5%)	15 (0.7%)	2 (0.1%)	31 (0.9%)
<b>Respiratory System</b>	214 (11.0%)	227 (12.0%)	162 (8.0%)	126 (7.6%)	353 (10.0%)
Cough	33 (1.7%)	31 (1.6%)	17 (0.8%)	8 (0.5%)	39 (1.1%)
Dyspnea	46 (2.4%)	49 (2.6%)	26 (1.3%)	18 (1.1%)	67 (1.9%)
Edema, pulmonary	16 (0.8%)	18 (1.0%)	26 (1.3%)	24 (1.4%)	42 (1.2%)
Rales/rhonchi	46 (2.4%)	54 (2.9%)	31 (1.5%)	23 (1.4%)	77 (2.2%)
<b>Skin and Skin Appendage</b>	127 (6.5%)	117 (6.2%)	91 (4.5%)	45 (2.7%)	162 (4.6%)
Rash	20 (1.0%)	17 (0.9%)	11 (0.5%)	9 (0.5%)	26 (0.7%)
Sweating	34 (1.7%)	24 (1.3%)	12 (0.6%)	2 (0.1%)	26 (0.7%)
<b>Special Senses</b>	20 (1.0%)	25 (1.3%)	16 (0.8%)	6 (0.4%)	31 (0.9%)
<b>Urogenital</b>	123 (6.3%)	122 (6.5%)	71 (3.5%)	49 (3.0%)	171 (4.8%)
Infection, urinary tract	38 (1.9%)	34 (1.8%)	24 (1.2%)	20 (1.2%)	54 (1.5%)
Urinary retention	10 (0.5%)	19 (1.0%)	6 (0.3%)	1 (0.1%)	20 (0.6%)

a. Data from NDA volume 1.2, Table C-37 and electronic datasets.

b. Includes all subjects from Heparin/ No procedures and Heparin/ Procedures groups.

### 6.2.2.10 Safety and Efficacy Measurements

The table below details the type and timing of the clinical information collected during the PRISM trial.

Table 6.2.2.10.1 Timing of clinical observations and laboratory measurements in the PRISM trial.

	Pre-infusion	Start infusion	6	12	24	Stop infusion	48	72	Day 7	Day 30
Time (hrs)		0								
Infusion										
ASA	X				X	X		X	X	X
History	X									
Physical	X				X	X		X		
ECG	X				X	X		X		
PT	X		X	X	X	X				
aPTT	X		X	X	X	X				
CPK with isoenzymes	X				X	X				
Laboratories <sup>a</sup>	X				X	X		X		
Hematology <sup>a</sup>			X							
Plasma tirofiban					X	X <sup>b</sup>				
Adverse Events (AEs)										
Endpoints/ Serious AEs										

a. Data from NDA volume 1.48, page 7063.

b. Plasma tirofiban level obtained 49-54 hours after start of infusion, after study drug termination.

c. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); urinalysis; and stool for occult blood.

### 6.2.2.11 Statistical Considerations

#### General statistical approach

Patients with multiple endpoints were counted only once in any analysis. The primary efficacy analyses and all safety analyses were performed on an intent-to-treat basis.

In addition, a selection of efficacy analyses were performed on a per-protocol basis. Patients were excluded from these analyses for the following reasons:

- Did not meet either inclusion criteria of accelerating pattern of anginal pain with electrocardiographic evidence of myocardial ischemia or recent onset of chest pain suggestive of myocardial ischemia and occurring at rest or with minimal effort.
- Did not meet inclusion criteria of most recent episode of chest pain within 24 hours of initiation of study drug, clinical evidence of underlying coronary artery disease, or 218 years of age.
- Did not take study drug, or D/C'd study drug in  $\leq 24$  hours without first experiencing a clinical endpoint.
- Incorrect initial diagnosis; e.g., pulmonary embolism or pericarditis.

The analysis of the pharmacokinetics substudy included only those subjects with tirofiban concentrations obtained at steady state to allow for calculation of systemic plasma clearance.

#### Analytical methods

1). For the clinical endpoint analyses, the statistical significance of the differences between treatment groups was assessed using a logistic regression analysis, using SAS.

2) The time course of the treatment effect was explored by Kaplan-Meier curves, and the difference between curves was assessed with a Cox regression model, using SAS.

3) The p-values for between-group comparisons for other variables were compared using Fisher's exact test, Chi-square test, and Wilcoxon rank-sum test as appropriate.

Details of the specific analyses performed can be found in NDA volume 1.48, reference 9, section 8. In this review, all statistical results are per the sponsor's analysis, unless otherwise specified.

#### Interim Analyses and sample size re-estimation

Two interim analyses were performed. Neither analysis met the prespecified guidelines for early termination using the O'Brien-Fleming boundary, and no recommendations were made regarding early discontinuation.

Initially, the interim analyses were to have taken place after 1/3 and 2/3 of the subjects had completed the trial. However, during the trial the rate of event accrual was lower than projected. The sponsor projected a 14.3% event rate in the heparin group, and a 30% reduction in events in the tirofiban group, for an average event rate of approximately 12%. Instead, the rate was 6% or less throughout the trial. For this reason, after the second interim analysis, the DSMB recommended an increase in the overall size of the trial to 3100 subjects (from 2000). This meant that the interim analyses took place before the 1/3 and 2/3 accrual marks.

## 6.2.2.12 Efficacy Outcomes

### 6.2.2.12.1 Patient Demographics & Baseline Characteristics

The next set of tables summarizes the baseline characteristics of the subjects enrolled in the trial.

Table 6.2.2.12.1.1 Demographics of the PRISM trial<sup>a</sup>.

Demographic	Tirofiban (n=1616)	Heparin (n=1616)	Combined (n=3232)
<b>Gender</b>			
Female	529 (32.7%)	505 (31.2%)	<b>1034 (32.0%)</b>
Male	1087 (67.3%)	1111 (68.8%)	2198 (68.0)
<b>Race</b>			
White	1349 (83.5%)	<b>1354 (83.8%)</b>	2703 (83.6%)
Black	86 (5.3%)	72 (4.5%)	158 (4.9%)
Asian	31 (1.9%)	39 (2.4%)	70 (2.2%)
Hispanic	83 (5.1%)	87 (5.4%)	170 (5.3%)
Other	67 (4.1%)	64 (4.0%)	131 (4.1%)
<b>Common Diagnosis</b>			
Hypertension	876 (54.2%)	882 (54.6%)	1758 (54.4%)
Hypercholesterolemia	767 (47.5%)	765 (47.3%)	1532 (47.4%)
Family Hx of heart disease	644 (39.9%)	673 (41.6%)	<b>1317 (40.7%)</b>
Hx of MI	756 (46.8%)	761 (47.1%)	1517 (46.9%)
Diabetes	329 (20.4%)	358 (22.2%)	687 (21.3%)
Tobacco Use	1105 (68.7%)	1126 (70.1%)	2231 (69.0%)
Anxiety	115 (7.1%)	111 (6.9%)	226 (7.0%)

a. Data from NDA volume 1.48, tables 7 and 8, based on all randomized subjects.

Table 6.2.2.12.1.2 Baseline physical examination and lab findings in the PRISM trial<sup>a</sup>.

Demographic	Tirofiban (n=1616)	Heparin (n=1616)	Combined (n=3232)
<b>Age (mean±sd)</b>	62.5±11.2	62.4±11.1	62.4±11.1
<b>Height (cm)</b>			
Males	172.9±7.7	172.3±7.5	172.6±7.6
Females	160.5±7.3	160.2±7.7	160.3±7.5
<b>Weight (kg)</b>			
Males	82.4±15.1	81.5±14.7	82.0±14.9
Females	71.4±14.9	72.1±16.1	71.7±15.5
<b>Supine BP</b>			
Systolic	132.6±21.3	132.5±20.5	132.5±20.9
Diastolic	76.2±12.2	76.9±12.5	76.6±12.4
<b>Pulse rate</b>	71.0±13.8	71.3±14.1	71.2±13.9

a. Data from NDA volume 1.48, tables 7, 8, and 9, based on all randomized subjects.

### 6.2.2.12.1 Patient Demographics & Baseline Characteristics (cont)

Table 6.2.2.12.1.3 Presenting clinical features in the PRISM trial<sup>a</sup>.

Demographic	Tirofiban (n=1616)	Heparin (n=1616)	Combined (n=3232)
<b>Presentation</b>			
NQWMI <sup>b</sup>	<b>391 (24.2%)</b>	412 (25.5%)	803 (24.8%)
Possible NQWMI	276 (17.1%)	291 (18.0%)	567 (17.5%)
Evolving NQWMI	115 (7.1%)	121 (7.5%)	236 (7.3%)
ECG signs of ischemia	828 (51.2%)	811 (50.2%)	1639 (50.7%)
History of CAD	366 (22.6%)	367 (22.7%)	733 (22.7%)
Unstable Angina Pectoris (UAP)	1225 (75.8%)	1204 (74.5%)	2429 (75.2%)
Other	31 (1.9%)	26 ( <b>1.6%</b> )	57 (1.8%)
<b>Specific ECG findings</b>			
No evidence of ischemia	475 (29.4%)	475 (29.4%)	<b>950 (29.4%)</b>
ECG evidence of ischemia	1141 (70.6%)	1141 (70.6%)	2282 (70.6%)
T-Wave inversion	811 (50.2%)	815 (50.4%)	1626 (50.3%)
ST segment depression	492 (30.4%)	503 (31.1%)	995 (30.8%)
ST segment elevation	119 (7.4%)	113 (7.0%)	232 (7.2%)
<b>Elapsed time from onset of pain to study start<sup>c</sup></b>			
<3 hours	246 (15.6%)	260 (16.4%)	506 (16.0%)
3 to 6 hours	338 (21.4%)	366 (23.1%)	704 (22.3%)
6 to 12 hours	182 (30.5%)	466 (29.4%)	948 (30.0%)
12 to 18 hours	250 (15.8%)	251 (15.9%)	501 (15.8%)
18 to 24 hours	241 (15.2%)	225 (14.2%)	466 ( <b>14.7%</b> )
>24 hours	24 (1.5%)	15 (0.9%)	39 (1.2%)
<b>Elapsed time from admission to study start<sup>c</sup></b>			
13 hours	370 (23.1%)	361 (22.5%)	731 (22.8%)
3 to 6 hours	405 (25.2%)	417 (36.0%)	822 (25.6%)
6 to 12 hours	249 ( <b>15.5%</b> )	270 (16.9%)	519 (16.2%)
12 to 18 hours	<b>175 (10.9%)</b>	153 (9.6%)	328 (10.2%)
18 to 24 hours	174 (10.8%)	176 ( <b>11.0%</b> )	350 ( <b>10.9%</b> )
>24 hours	232 (14.4%)	224 (13.9%)	456 (14.1%)

a. Data from NDA volume 1.48, table 5.

b. Includes both 'possible' and 'evolving' NQWMI.

c. Data includes only those subjects with available data.

### 6.2.2.12.2 Disposition and Follow-up of Subjects

#### Disposition

The table below summarizes the disposition of the subjects enrolled in the PRISM trial, including the reasons for subject discontinuation. Significantly more subjects in the heparin alone group were discontinued after meeting one of the clinical endpoints (refractory cardiac ischemia, new myocardial infarction or death).

Table 6.2.2.12.2.1 Disposition of subjects randomized in the PRISM trial<sup>a</sup>.

Patient Disposition	Tirofiban	Heparin	Total
<b>Randomized</b>	1616	1616	3232
<b>Completed</b>	1423 (88%) <sup>b</sup>	1432 (89%)	2855 (88%)
<b>Discontinued (Total)</b>	193 (12%)	184 (11%)	377 (12%)
Presumed clinical endpoint <sup>b</sup>	51 (3.2%)	76 (4.7%)	127 (3.9%)
Nonbleeding clinical AE <sup>c</sup>	19 (1.2%)	13 (0.8%)	32 (1.0%)
Nonbleeding laboratory AE <sup>c</sup>	7 (0.43%)	1 <sup>e</sup> (0.06%)	8 (0.2%)
Bleeding clinical or lab AE <sup>d</sup>	18 (1.1%)	10 (0.6%)	28 (0.86%)
Patient noncompliance	3 (0.2%)	4 (0.2%)	7 (0.2%)
Protocol deviation	45 (2.8%)	43 (2.7%)	88 (2.7%)
Patient withdrawn	20 (1.2%)	10 (0.6%)	30 (0.9%)
Did not receive drug	27 (1.7%)	25 (1.5%)	52 (1.6%)
Other reasons	3 (0.2%)	2 (0.1%)	5 (0.2%)

a. Data from NDA volume 1.48, page 7037 and electronic datasets. Shown is % of subjects randomized.

b. There was a significant difference between the two groups with respect to discontinuations due to presumed clinical endpoints (p=0.029 per the sponsor's analysis).

c. Includes subjects who discontinued due to nonbleeding clinical or nonbleeding laboratory adverse events.

d. Includes clinical or laboratory discontinuations.

e. AN2171 discontinued study drug due to AE lab value, but no AE was provided to sponsor.

### 6.2.2.12.2 Disposition and Follow-up of Subjects (cont)

#### Subject follow-up in the PRISM trial

The FDA also analyzed the extent of follow-up for subjects in each of the treatment groups, to gauge the adequacy of the clinical database. The following tables give descriptive statistics on length of follow-up for the patients who survived 30 days after randomization. The treatment groups were comparable with respect to the duration of follow-up, and >95% of the subjects had follow-up for at least 30 days.

Table 6.2 12.2.2 Summary statistics on duration of follow-up in PRISM trial<sup>a</sup>.

	Tirofiban alone n=1534	Heparin n=1530
<30 days	4.4%	3.1%
≥30 days	95.6%	96.9%
mean±sd	139±21	40±27
range	1-448	2-709
99th percentile	113	114
95th percentile	67	68
75th percentile	39	40
50th percentile	33	34
25th percentile	31	31
5th percentile	30	30
1st percentile	28	29

a. Data shown for 30 days survivors, collected from electronic datasets by FDA.

#### 6.2.2.12.2a Subject Selection

No information is available to this reviewer regarding the selection of subjects for this trial.

#### 6.2.2.12.2b Protocol Violations & Deviations

The primary analysis of the PRISM trial results was based on all randomized subjects (Intent-to-Treat analysis), and included 3232 subjects. A second, 'per-protocol' analysis was also performed by the sponsor, which excluded 206 subjects for reasons detailed in the statistical section above (6.2.2.1 I). A summary of these discontinuations is shown below.

Table 6.2.2.12.2b.1 Reasons for subject exclusion from 'per protocol' analyses in PRISM trial<sup>a</sup>.

Reason for exclusion	Tirofiban n=1616	Heparin n=1616
Excluded for any reason	112 (6.9%)	94 (5.8%)
Excluded for failure to meet inclusion criteria	26 (1.6%)	26 (1.6%)
Excluded for no study drug received	27 (1.7%)	25 (1.5%)
Excluded for <24 hrs of study drug received	64 (4.0%)	48 (3.0%)

a. Data from NDA 20-912, volume 1.48, ref. 9, tables 11.

#### 6.2.2.12.2c Concomitant Therapies used after Trial Initiation

The median length of hospital stay was 7 days in both groups. The mean length of stay, measured from the start of the study to the time of hospital discharge were similar between the two groups: tirofiban alone, 10.0±9.9 (range from 0 to 145 days); and heparin alone 9.5±8.6 (range from 0 to 111 days, p=0.60).

The time from onset of pain until receipt of study drug was <6 hours in approximately 35.4% of all subjects, as seen from the table below. These results are similar to those seen in the PRISM-PLUS trial (see table 6.2.1.12.1c.1).

Table 6.2.2.12.2c.1 Time to administration of study drug after onset of pain in the PRISM study<sup>a</sup>.

Elapsed time (hrs)	Tirofiban n=1616	Heparin n=1616	Total n=3232
<3 hours	246 (15.6%)	260 (16.4%)	506 (16.0%)
3 to 6 hours	338 (21.4%)	366 (23.1%)	704 (22.3%)
6 to 12 hours	482 (30.5%)	466 (29.4%)	948 (30.0%)
12 to 18 hours	250 (15.8%)	251 (15.9%)	501 (15.8%)
18 to 24 hours	241 (15.2%)	225 (14.2%)	466 (14.7%)
>24 hours	24 (1.5%)	15 (0.9%)	39 (1.2%)

a. Data from NDA volume 1.48, ref. 9, table 5.

### 6.2.2.12.2c Concomitant Therapies used after Trial Initiation (cont)

Subjects in this trial received infusions of either tirofiban (or it's placebo) or heparin (or it's placebo), as well as a bolus of heparin, administered to all subjects undergoing PTCA/ angioplasty. The duration of these study drug infusions were similar among the three groups, as shown in the table below.

Table 2.2.12.2c.2 Duration of study drug infusion in the "PRISMtrial".

Duration of study drug administration (hrs)	Tirofiban n=1616	Heparin n=1616	J-value
<b>Tirofiban/ Placebo</b>			
No drug	27 (1.7%)	25 (1.5%)	
24 hours	<b>95 (5.9%)</b>	72 (4.5)	
24-47 hours	186 (11.5%)	<b>209 (12.9%)</b>	
248 hours	1308 (80.9%)	<b>1310 (81.1%)</b>	
<b>Mean±SD</b>	45.6±8.7	<b>46.0±8.0</b>	<b>0.81</b>
<b>Heparin/ Placebo</b>			
No drug	28 (1.7%)	27 (1.7%)	
24 hours	94 (5.8%)	72 (4.5%)	
24-47 hours	203 (12.6%)	234 (14.5%)	
248 hours	<b>1291 (79.9%)</b>	1283 (79.4%)	
<b>Mean±SD</b>	<b>45.6±8.7</b>	<b>45.9±8.1</b>	0.56

a. Data from NDA 20-912, volume 1.48, ref. 9, tables 13.

The heparin group did, however, receive a larger number of boluses from the heparin/placebo bags.

Table 6.2.2.12.2c.3 Number of heparin/placebo boluses administered in the PRISM trial".

Duration of study drug administration (hrs)	Tirofiban n=1616	Heparin n=1616	p-value
<b>Non-angiography vial</b>			
0	76 (4.7%)	60 (3.7%)	
	<b>1134 (70.2%)</b>	913 (56.5%)	
2	<b>296 (18.3%)</b>	347 (21.5%)	
3	88 (5.4%)	193 (11.9%)	
4	11 (0.7%)	70 (4.3%)	
5	10 (0.6%)	25 (1.5%)	
16	<b>1 (0.1%)</b>	8 (0.5%)	
<b>Mean(SD)</b>	1.3±0.7	<b>1.6±1.1</b>	0.001
<b>4ngiography vial</b>			
0	1425 (88.2%)	1407 (87.1%)	
	190 (11.8%)	208 (12.9%)	
2	1 (0.1%)	1 (0.1%)	
<b>Mean(SD)</b>	<b>0.1±0.3</b>	<b>0.1±0.3</b>	0.34

a. Data from NDA 20-912, volume 1.48, ref. 9, table 14.

As expected, there was a significant difference between the two groups with regard to aPTT, measured at hours 6, 12, 24, and 48 after start of study drug administration. At all four time points, between 10 and 20% of the heparin subjects had aPTTs <45 seconds (the therapeutic target for the study), while <5% of the tirofiban subjects had aPTT >245 seconds. Some individuals in the heparin group did have prolonged aPTTs at all time points (data below is for the 12 and 24 hour time points only).

### 6.2.2.12.2c Concomitant Therapies used after Trial Initiation (cont)

The number of subjects with prolonged aPTT was also much greater in the heparin group.

Table 6.2.2.1 Table 4 Number of subjects with prolonged aPTT in the PRISM trial<sup>a</sup>.

aPTT (secs)	Tirofiban n=1616	Heparin n=1616
<b>Hour 12</b>		
<30 secs	874 (57.8%)	30 (1.8%)
30-45 secs	590 (39.0%)	176 (10.5%)
46-60 secs	41 (2.7%)	425 (25.5%)
60-85 secs	4 (0.3%)	616 (36.9%)
86-120 secs	2 (0.1%)	266 (15.9%)
>120 secs	2 (0.1%)	156 (9.3%)
<b>Mean±SD</b>	<b>29.8±7.5</b>	<b>74.3±34.5</b>
<b>Hour 24</b>		
<30 secs	1140 (60.8%)	64 (2.6%)
30-45 secs	690 (36.8%)	378 (15.1%)
46-60 secs	36 (1.9%)	713 (28.4%)
60-85 secs	8 (0.4%)	834 (33.3%)
86-120 secs	1 (0.1%)	328 (13.1%)
>120 secs	1 (0.1%)	191 (7.6%)
<b>Mean±SD</b>	<b>29.2±7.4</b>	<b>69.0±32.2</b>

a. Data from ref. 9, appendix 4.1.6 and electronic datasets.

Concomitant medications were taken by almost all subjects (>99%). The most common other medications include beta-blockers (71%), calcium channel blockers (47%), nitrates (85%), and ASA (97%). The two study groups were not significantly different with regard to their use of these medications with the exception of glyburide, which was used more frequently in the heparin group (6.6% vs. 4.8%, p=0.040 nominally). Diabetes was not more common in the heparin group (22.2% vs. 20.4%).

### 6.2.2.12.2d Primary Analyses of the PRISM Trial Results

The primary endpoint of the PRISM trial was the incidence of refractory ischemia (RI), new myocardial infarction or death at 48 hours of study drug infusion. The incidence of the same endpoint at 7 and 30 days were pre-specified secondary and supportive endpoints respectively. The table below summarizes the results for the composite endpoint and its parts at these three endpoints. Also included are the odds ratio (shown in bold) with its 95% confidence interval (CI) and the p value (verified by the FDA). No data at the end of 180 days was collected in this trial. The primary endpoint of the PRISM trial was the incidence of refractory ischemia (RI), new MI, or death at 48 hours of study drug infusion. The proportions of subjects who met the composite endpoint at 48 hours was 61/1616 (3.8%) in the tirofiban group and 91/1616 (5.6%) in the heparin group. This difference between treatments has an odds ratio of 0.659, which represents a 33% risk reduction for an event in the tirofiban group (p=0.014). The incidence of the same endpoint at 7 and 30 days were pre-specified secondary and supportive endpoints respectively.

#### 6.2.2.12.2d.1 Incidence of the primary endpoint and its components at 48 hours, 7 and 30 days in the PRISM trial<sup>a</sup>.

	Tirofiban n=1616	Heparin n=1616	Odds ration (bold) & 95% CI	p value <sup>b</sup>
<b>Combined endpoint at 48 hours (primary endpoint)</b>	61 (3.8%)	91 (5.6%)	<b>0.659</b> 0.473, 0.919	0.014
<b>Combined endpoint at 7 days</b>	166 (10.3%)	182 (11.3%)	<b>0.903</b> 0.722, 1.130	0.37
<b>Combined endpoint at 30 days</b>	257 (15.9%)	276 (17.1%)	<b>0.919</b> 0.763, 1.108	0.38
<b>RI at 48 hours</b>	56 (3.5%)	86 (5.3%)	<b>0.640</b> 0.453, 0.903	0.011
<b>RI at 7 days</b>	147 (9.1%)	160 (9.9%)	<b>0.913</b> 0.721, 1.156	0.45
<b>RI at 30 days</b>	172 (10.6%)	174 (10.8%)	<b>0.992</b> 0.793, 1.241	0.94
<b>MI (both fatal and non-fatal) at 48 hours</b>	14 (0.9%)	22 (1.4%)	<b>0.639</b> 0.325, 1.254	0.19
<b>MI (both fatal and non-fatal) at 7 days</b>	42 (2.6%)	50 (3.1%)	<b>0.837</b> 0.552, 1.270	0.40
<b>MI (both fatal and non-fatal) at 30 days</b>	66 (4.1%)	69 (4.3%)	<b>0.957</b> 0.677, 1.352	0.80
<b>Death at 48 hours</b>	6 (0.4%)	4 (0.2%)	1.488 0.419, 5.289	0.54
<b>Death at 7 days</b>	16 (1.0%)	25 (1.6%)	0.630 0.335, 1.185	0.15
<b>Death at 30 days</b>	37 (2.3%)	59 (3.6%)	0.612 0.403, 0.930	0.021

a. Data from NDA 20-912, volume 1.48, tables 20-25. Intent-to-treat population is used.

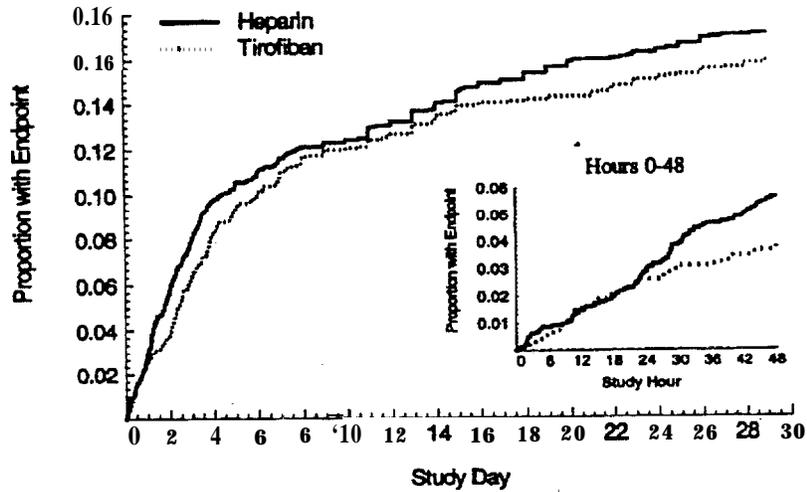
b. p value per the sponsor based on logistic regression analysis, confirmed by FDA analysis.

c. RI: refractory cardiac ischemia. These included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, or (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes.

**6.2.2.12.2d Primary Analyses of the PRISM Trial Results (cont)**

The sponsor also analyzed the incidence of the primary endpoint according to time after entry into the study, and that graph is shown below.

Figure 6.2.2.12.2d.1 Incidence of combined endpoint (MI/Death/ Refractory Ischemia) for up to 30 days in the PRISM trial.



The FDA also performed a post-hoc analysis of the incidence of the primary endpoint and Death/ MI using Pearson’s chi square.

6.2.2.12.2d.2 Incidence of the primary endpoint and Death/ MI at 48 hours, 7 and 30 days in the PRISM trial, analyzed using chi square.

	Tirofiban n=1616	Heparin n=1616	pvalue by chi square <sup>b</sup>
<b>Combined endpoint at 48 hours (primary endpoint)</b>	<b>61 (3.8%)</b>	<b>91 (5.6%)</b>	<b>0.0127</b>
<b>Combined endpoint at 7 days</b>	<b>166 (10.3%)</b>	<b>182 (11.3%)</b>	<b>0.36</b>
<b>Combined endpoint at 30 days</b>	<b>257 (15.9%)</b>	<b>276 (17.1%)</b>	<b>0.37</b>
<b>MI/Death at 48 hours</b>	<b>19 (1.2%)</b>	<b>25 (1.5%)</b>	<b>0.37</b>
<b>MI/Death at 7 days</b>	<b>53 (3.3%)</b>	<b>68 (4.2%)</b>	<b>0.17</b>
<b>MI/Death at 30 days</b>	<b>93 (5.8%)</b>	<b>115 (7.1%)</b>	<b>0.12</b>

a. Data from NDA 20-912, volume 1.48, tables 20-25. Intent-to-treat population is used.

b. p value per the FDA based using Pearson’s chi square,

c. RI: refractory cardiac ischemia. These included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, or (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes.

### 6.2.2.12.3 Subgroup & Post-hoc Analyses of the PRISM Trial Results

#### Other outcomes: analysis of the primary endpoint using the 'per-protocol' population

The primary endpoint and its components were also analyzed on a per-protocol population, as detailed in the statistical section above. This analysis excludes subjects who did not receive study drug, or received it for <24 hrs before discontinuation (without meeting a clinical endpoint). The results are consistent with the primary analysis.

Table 6.2.2.12.3.1 Incidence of endpoints from the PRISM trial for the 'per-protocol' population<sup>a</sup>.

Results at 48 hours	Tirofiban n=1504	Heparin n=1522	p value <sup>b</sup>
<b>Primary endpoint (RI,MI,Death)<sup>c</sup></b>	59 (3.9%)	85 (5.6%)	0.033
<b>RI</b>	55 (3.7%)	82 (5.4%)	0.023
<b>MI (both fatal and non-fatal)</b>	13 (0.9%)	20 (1.3%)	0.24
<b>Death</b>	5 (0.3%)	4 (0.3%)	0.73

a. Data from ref. 9, appendix 4.1.8.

b. p value per the sponsor based on logistic regression analysis.

c. RI: refractory ischemia.

#### Other outcomes: analysis of the primary endpoint according to procedures received during initial hospitalization

The sponsor prespecified an analysis of the composite endpoint based on the procedures received during the trial. These analyses were also performed in the PRISM-PLUS trial. Also included is an analysis of the effect of tirofiban on fatal MIs at the end of 48 hours.

1. The 'primary endpoint/ procedure' group includes all subjects who had experienced RIC and underwent one or more of the following procedures: angiography; angioplasty; atherectomy; stent placement; CABG or IABP.

2. The 'primary endpoint/ revascularization' group includes all subjects who had experienced RIC and underwent one or more of the following procedures: angioplasty; CABG; atherectomy; or stent placement.

Table 6.2.2.12.3.2 Incidence of endpoints from the PRISM trial according to procedures received<sup>a</sup>.

Results at 48 hours	Tirofiban n=1616	Heparin n=1616	p value <sup>b</sup>
<b>MI (fatal only)</b>	4 (0.2%)	5 (0.2%)	0.75
<b>Primary endpoint/ procedure<sup>d</sup></b>	48 (3.0%)	75 (4.6%)	0.015
<b>Primary endpoint/ revascularization<sup>e</sup></b>	38 (2.4%)	63 (3.9%)	0.013

a. Data from NDA 20-912, volume 1.48, table 20. Intent-to-treat population is used.

b. p value per the sponsor based on logistic regression analysis.

c. RI: refractory cardiac ischemia.

d. Includes the subjects who met the primary endpoint and also had a cardiac procedure performed.

e. Included the subjects who met the primary endpoint **and** also had a revascularization procedure performed.

#### Other outcomes: analysis of primary endpoint in subjects who developed refractory ischemia

The sponsor suggested that subjects who develop refractory ischemia during their initial hospitalization are at higher risk for subsequent cardiac events. Refractory ischemia includes subjects with recurrent anginal pain despite maximal medical management and hemodynamic instability in the setting of angina or ECG changes. The sponsor first analyzed those subjects who developed RI within 48 hours of starting the study. Note that these subjects represent an extremely small % of the total number of subjects (56/1616, 3.5% of the total tirofiban group, 85/1616 5.3% of the total heparin group). No statistical analysis is attempted given the post-hoc nature and small subject numbers. While the incidence of MI is higher in the tirofiban group, the incidence of cardiac interventions of all kinds was decreased in the tirofiban group.

Table 6.2.2.12.3.3 Incidence of endpoints during subsequent 48 hours in subjects who develop R within 48 hours of starting the PRISM trial<sup>a</sup>.

Results at 48 hours	Tirofiban n=56	Heparin n=85
<b>Death</b>	5 (8.9%)	6 (7.1%)
<b>Myocardial infarction</b>	12 (21.4%)	14 (16.5%)
<b>Coronary angiography</b>	22 (39.3%)	44 (51.8%)
<b>IABP</b>	9 (16.1%)	8 (9.4%)
<b>Revascularizations</b>	12 (21.4%)	27 (31.8%)
<b>Death/MI</b>	15 (26.8%)	18 (21.2%)
<b>Any of the above</b>	32 (57.1%)	56 (65.9%)

a. Data from NDA 20-912, volume 1.48, table 24.

### 6.2.2.12.3 Subgroup & Post-hoc Analyses of the PRISM Trial Results (cont)

#### Other outcomes: analysis of frequency of angina

The occurrence of angina during the initial hospitalization was recorded by the investigators per protocol. Subject in the tirofiban group had fewer episodes of angina during the first 48 hours of the study (roughly, during the study drug infusion):  $0.6 \pm 1.2$  vs.  $0.7 \pm 2.0$  episodes per subject,  $p=0.006$  per sponsor's analysis. From 48 hours to time of discharge, the heparin group had significantly fewer episodes of angina than the tirofiban group:  $0.7 \pm 1.9$  vs.  $0.8 \pm 2.0$  episodes per subject,  $p=0.024$  per sponsor's analysis). There was no difference between the two groups with regard to the number of angina attacks during the entire hospitalization.

#### Analysis of frequency of cardiac procedures

A potential benefit of tirofiban would be the reduction in the use of cardiac procedures following its use. The occurrence of cardiac procedures was collected during the initial 30 day period, and a comparison of the types and frequencies between the tirofiban and heparin groups appears below. No significant differences were detected.

Table 6.2.2.12.3.4 Cardiac procedures during first 30 days of the PRISM trial<sup>a</sup>.

Procedure	Tirofiban n=1616	Heparin n=1616	p value <sup>b</sup>
Any cardiac procedure	1072 (66.3%)	1062 (65.7%)	0.74
Angiography	998 (61.8%)	1005 (62.2%)	0.83
Any revascularization	624 (38.6%)	609 (37.7%)	0.61
Angioplasty	320 (19.8%)	334 (20.7%)	0.57
Atherectomy	11 (0.7%)	10 (0.6%)	0.99
Stent	123 (7.6%)	99 (6.1%)	0.11
CABG	296 (18.3%)	269 (16.6%)	0.23
IABP	43 (2.7%)	31 (1.9%)	0.20
# of procedures per subject (mean $\pm$ SD)	1.16 $\pm$ 1.10	1.14 $\pm$ 1.10	0.60

a. Data from NDA 20-912, volume 1.48, table 24.

b. p value per the sponsor based on logistic regression analysis.

#### Analysis of clinical events following PTCA during initial hospitalization

The sponsors performed a post-hoc analysis of the subsequent clinical events that occurred to subjects in the PRISM trial who had a PTCA, in part mirroring the population studied in the RESTORE trial. Note, however, that in the PRISM trial only 10 subjects received their PTCA during their tirofiban infusion. The subjects who had PTCA represents a minority population of the entire PRISM trial: 320/1616 (19.8%) of the total tirofiban group; 334/1616 (20.7%) of the total heparin group. The demographics of the PTCA population of the PRISM trial are discussed in Appendix 10, section 22.0.

The table below presents the incidence of the composite endpoint and its components for the following groupings:

Patients who underwent PTCA:

- 1) Incidence rates over the entire 30-day period (that is, from Day 1 to Day 30).
- 2) Incidence rates prior to the PTCA (that is, from study Day 1 until the time of PTCA).
- 3) Incidence rates following PTCA through Day 30 (that is, from the time of PTCA through Day 30

of the study).

Patients who did not undergo PTCA during the initial hospitalization:

- 1) Incidence rates over the entire 30-day period (that is, from Day 1 to Day 30).

The shaded boxes highlight the post-PTCA subgroup. In all subgroups, the incidence of the composite endpoint and its components was lower in the tirofiban group, compared with heparin. Note that for the subjects who did not undergo PTCA, the event rates were quite low, and there was little or no difference between the tirofiban and heparin group event rates for the composite endpoint or for MI.

6.2.2.12.3 Subgroup & Post-hoc Analyses of the PRISM Trial Results (cont)

Table 6.2.2.12.3.5 Clinical events during the first 30 days grouped according to receipt of PTCA in the PRISM trial<sup>a</sup>.

Procedure	Tirofiban	Heparin
<b>Composite Endpoint (RIC, MI, Death)</b>		
All subjects	257/1616 (15.9%)	276/1616 (17.1%)
Subjects who underwent PTCA	71/320 (22.2%)	94/334 (28.1%)
Prior to PTCA only	50/320 (15.6%)	73/334 (21.9%)
Subsequent to PTCA only	27/320 (8.4%)	35/334 (10.5%)
Subjects who did not undergo PTCA	186/1296 (14.4%)	182/1282 (14.2%)
<b>MI (fatal/ nonfatal)</b>		
All subjects	66/1616 (4.1%)	69/1616 (4.3%)
Subjects who underwent PTCA	22/320 (6.9%)	25/334 (7.5%)
Prior to PTCA only	14/320 (4.4%)	15/334 (4.5%)
Subsequent to PTCA only	8/320 (2.5%)	10/334 (3.0%)
Subjects who did not undergo PTCA	44/1296 (3.4%)	44/1282 (3.4%)
<b>Death</b>		
All subjects	37/1616 (2.3%)	59/1616 (3.6%)
Subjects who underwent PTCA	1/320 (0.3%)	7/334 (2.1%)
Prior to PTCA only	0/320 (0.0%)	0/334 (0.0%)
Subsequent to PTCA only	1/320 (0.3%)	7/334 (2.1%)
Subjects who did not undergo PTCA	36/1296 (2.8%)	52/1282 (4.1%)

a. Data from NDA 20-912, volume 1.42, reference 5, table 27, adjoining text, and from personal communication with sponsor.

The table above summarizes clinical events that occurred during the first 30 days after start of the study. This means that an individual who had PTCA on day 23 (for example) would have follow-up information for only an additional 7 days. The FDA performed a similar analysis looking at events that occurred during the first 7 days after PTCA, where a larger % of the subjects have data for all 7 days. This is presented only for those subjects who received PTCA, since they are the only group affected by the 30 day cut-off for follow-up (those who did not get PTCA have clinical event data for an entire 30 days).

Table 6.2.1.12.3.6 Clinical events in during the first 7 days following receipt of PTCA in th PRISMtrial<sup>a</sup>.

Clinical endpoint	Tirofiban n=320/1616 (19.8% of total)	Heparin n=334/1616 (20.7% of total)
Composite Endpoint (RIC, MI, Death)	12 (3.8%)	13 (3.9%)
MI (fatal/ nonfatal)	7 (2.2%)	9 (2.7%)
Death	1 (0.3%)	4 (1.2%)

a. Data from electronic datasets and SAS analysis per FDA,

### 6.2.2.12.3 Subgroup & Post-hoc Analyses of the PRISM Trial Results (cont)

#### Pre-specified subgroup analyses of the PRISM primary endpoint

The sponsor performed a large number of exploratory analyses to investigate the effects of tirofiban in various subject subgroups, and those results are shown below. The incidence of the primary endpoint was high in both groups of subjects >75 years of age, and in subjects entering the trial with ECG evidence of ischemia.

Table 6.2.2.12.3.6 Incidence of the combined endpoint and its components at 48 hours in various subgroups from the PRISM trial<sup>a</sup>.

	Tirofiban n=1616	Heparin n=1616
<b>Age</b>		
<65	25/884 (2.8%)	36/899 (4.0%)
65 to 74	18/502 (3.6%)	29/502 (5.8%)
≥75	18/230 (7.8%)	26/215 (12.1%)
≥65	36/732 (4.9%)	55/717 (7.7%)
<b>Gender</b>		
Female	20/529 (3.8%)	35/505 (6.9%)
Male	41/1087 (3.8%)	56/1111 (5.0%)
<b>Race</b>		
White	50/1349 (3.7%)	78/1354 (5.8%)
Black	2/86 (2.3%)	3/72 (4.2%)
Hispanic	3/83 (3.6%)	7/87 (8.0%)
Other	6/98 (6.1%)	3/103 (2.9%)
<b>Weight</b>		
Light (<75 kg)	30/677 (4.4%)	39/662 (5.9%)
75 to 85 kg	19/455 (4.2%)	28/1497 (5.6%)
Heavy (>85 kg)	12/482 (2.5%)	24/455 (5.3%)
<b>Presentation</b>		
Possible/evolving MI	19/391 (4.9%)	34/412 (8.2%)
ECG evidence	27/828 (3.3%)	51/811 (6.3%)
Hx of CAD	15/366 (4.1%)	6/367 (1.6%)
<b>Aspirin Prestudy</b>		
Yes	42/940 (4.5%)	51/968 (5.3%)
No	19/676 (2.8%)	40/648 (6.2%)
<b>Beta-blocker Prestudy</b>		
Yes	35/1841 (4.2%)	51/850 (6.0%)
No	26/775 (3.4%)	40/766 (5.2%)
<b>Calcium channel-blocker Prestudy</b>		
Yes	34/721 (4.7%)	40/742 (5.4%)
No	27/895 (3.0%)	51/874 (5.8%)
<b>ECG evidence of ischemia</b>		
S-T depression	27/492 (5.5%)	51/503 (10.2%)
S-T elevation	4/117 (3.4%)	4/110 (3.6%)
T-wave inversion	3/91 (3.3%)	3/86 (3.5%)
<b>NQWMI</b>		
Possible	12/276 (4.4%)	21/291 (7.2%)
Evolving	7/115 (6.1%)	13/121 (10.7%)
Unstable angina	42/1225 (3.4%)	57/1204 (4.7%)
<b>Risk category</b>		
High	35/1784 (4.5%)	62/793 (7.8%)
Low	26/832 (3.1%)	29/823 (3.5%)
<b>Diabetes</b>		
Yes	12/382 (3.7%)	25/357 (7.0%)
<b>Smoking status</b>		
Never	21/557 (3.8%)	41/524 (7.8%)
Ex-smoker	23/628 (3.7%)	26/655 (4.0%)
Current smoker	17/419 (4.1%)	23/423 (5.4%)
<b>Heparin Prestudy</b>		
No	46/1197 (3.8%)	67/1184 (5.7%)

a. Data from NDA 20-912, volume 1.48, ref 9, tables 21. Intent-to-treat population is used. NA= not applicable

### 6.2.2.12.3 Subgroup & Post-hoc Analyses of the PRISM Trial Results (cont)

#### Pharmacokinetics of tirofiban

Plasma tirofiban concentrations were available for 762 subjects, on which the sponsor performed a subset analysis looking at tirofiban pharmacokinetics. The mean plasma clearance (Cl<sub>r</sub>) was 177±84 ml/min. The first tables summarize the clearance data according to age and then by renal function (clearance calculated using Cochrift-Gault formula).

Table 6.2.2.12.3.7 Tirofiban clearance during PRISM according to subject age<sup>a</sup>.

	≤65 years	165 years	Difference	p-value & (95%CI)
Cl <sub>r</sub> (mllmin)	195.09±89	147.9±65	-47.2	<0.001 (-59, -35.4)

a. Data from NDA volume 1.48, ref. 9, table 15.

There was a highly significant interaction between calculated creatinine clearance and plasma tirofiban clearance (p<0.001 by ANOVA). When expressed by the fraction of the normal clearance (≥75 ml/min), subjects with creatinine clearance rates <30 ml/min have a clearance rate for tirofiban of approximately 50% of normal. Note the small number of subjects with extremely diminished creatinine clearances.

Table 6.2.2.12.3.8 Tirofiban clearance during PRISM according to calculated creatinine clearance<sup>a</sup>.

	<30 mllmin n=12	30-60 mllmin n=246	61-74 mllmin n=193	275 mllmin n=299
Cl <sub>r</sub> (ml/min)	94.98±42.1	146.4±67	174.99±84.7	207.31±86.5
Cl <sub>r</sub> (ml/min) expressed as % of ≥75 mllmin Cl <sub>r</sub>	45.8%	70.5%	84.5%	--

a. Data from NDA volume 1.48, ref. 9, table 16, and calculated by medical reviewer.

The sponsor also examined the effect of race and gender on tirofiban clearance. No effect of either race or gender on tirofiban clearance was detected.

Table 6.2.2.12.3.9 Tirofiban clearance during PRISM according to subject race<sup>a</sup>.

	White n=613	Non-white n=149
Cl <sub>r</sub> (ml/min)	178.5±86.8	170.7±71
<u>Non-whites</u>		
Asian (n=5)		144.6±35
Black (n=47)		172.7±58
Hispanic (n=54)		175.9±92
Other (n=43)		165.1±55.4

a. Data from NDA volume 1.48, ref. 9, table 17.

Table 6.2.2.12.3.10 Tirofiban clearance during PRISM according to subject gender<sup>a</sup>.

	Male n=504	Female n=258
Cl <sub>r</sub> (mllmin)	179.4±76.2	172.2±97.4

a. Data from NDA volume 1.48, ref. 9, table 18.

#### Effect of concomitant medications on the plasma tirofiban clearance

The sponsor performed a series of post-hoc analyses, examining the effects of individual concomitant medications on the tirofiban clearance. After adjusting for multiple comparisons, the only significant differences between subjects receiving/ not receiving tirofiban was for the following two drugs: levothyroxine (Cl<sub>r</sub> 175.3 ml/min without levothyroxine, 218.5 mllmin with, p<0.001); and omeprazole (176.0 ml/min without omeprazole, 252.1 ml/min with, p<0.001). The sponsor argues that since, in both cases, the tirofiban clearance is higher in the group taking the drug, no impact on subject safety can be expected.

### 6.2.2.13 Safety Outcomes

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters from the PRISM trial: deaths; subject discontinuations; bleeding AEs; and thrombocytopenia. The first table summarizes the adverse clinical events that occurred in the PRISM trial within the first 30 days. The tirofiban group had more AEs thought to be drug-related by the investigators, more serious and drug-related AEs, more discontinuations of all types due to AEs, and more discontinuations for bleeding AEs, when compared with the heparin alone group.

Table 6.2.2.13.1 Clinical adverse experience (AE) summary from the PRISM trial<sup>a</sup>.

Clinical event	Tirofiban n=1616	Heparin n=1616	p value
With any AE	883 (54.6%)	837 (51.8%)	0.11
Without any AE	733 (45.4%)	779 (48.2%)	0.11
With Serious AE (SAE)	292 (18.1%)	293 (18.1%)	0.99
With drug-related AE <sup>b</sup>	247 (15.3%)	143 (8.8%)	<0.001
With serious and drug-related AEs	18 (1.1%)	4 (0.2%)	0.004
Discontinued due to an AE	36 (2.2%)	19 (1.2%)	0.029
Discontinued due to a bleeding AE	17 (1.1%)	6 (0.4%)	0.034
Discontinued due to lab AE	8 (0.5%)	5 (0.3%)	0.58
Deaths <sup>d</sup>	40 (2.5%)	62 (3.8%)	0.034

a. Data from NDA volume 1.42, ref. 5, table 32, and electronic datasets.

b. Felt to be possibly, probably, or definitely drug-related by individual investigators.

c. p value calculated using chi square analysis by the sponsor.

d. Counts deaths that occurred prior to closure of the 30-day safety database, including 6 subjects who died after 30 days (3 in each treatment group).

#### 6.2.2.13.1 Comparisons of Defined Safety Endpoints

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters from the PRISM trial: deaths; subject discontinuations; bleeding AEs; and thrombocytopenia.

#### 6.2.2.13.2 Comments on Specific Safety Parameters

##### Deaths

Through 30 days of follow-up, 96 subject deaths were reported for PRISM. Per protocol, no 180 day follow-up data was collected.

Table 6.2.2.13.2.1 Deaths in the PRISM trial<sup>a</sup>

Time of Follow-up	Tirofiban n=1616	Heparin n=1616	Total n=3232
48 hours	6 (0.4%)	4 (0.2%)	10 (0.3%)
7 days	16 (1.0%)	25 (1.6%)	41 (1.3%)
30 days	37 (2.3%)	59 (3.6%)	96 (3.0%)

a. Data from NDA volume 1.48, reference 9, tables 20-27.

Subject death narratives from PRISM are included in appendix two (section 14.0).

### 6.2.2.13.2 Comments on Specific Safety Parameters (cont)

#### Subject discontinuations

As shown above, more subjects in the tirofiban group were discontinued for bleeding AEs. The next table summarizes the major causes for subject discontinuations in the PRISM trial.

Table 6.2.2.13.2.2 Significant clinical AEs leading to discontinuation in the PRISM trial<sup>a</sup>.

	Tirofiban alone n=1616	Heparin alone n=1616	p value <sup>b</sup>
<b>Any Adverse Experience (resulting in discontinuation)</b>	36 (2.2%)	19 (1.2%)	0.029
<b>Body as a Whole/Site Unspecified)</b>	4 (0.2%)	2 (0.1%)	0.69
<b>Cardiovascular System</b>	7 (0.4%)	5 (0.3%)	0.77
<b>Digestive System</b>	11 (0.7%)	3 (0.2%)	0.057
Fecal occult blood	1 (0.1%)	0 (0%)	0.99
Hemorrhage, anal/rectal	2 (0.1%)	0 (0%)	0.50
Hemorrhage, gastrointestinal	2 (0.1%)	0 (0%)	0.50
Hemorrhage, GI-lower	1 (0.1%)	0 (0%)	0.99
Melena	2 (0.1%)	0 (0%)	0.50
Ulcer, gastric, with hemorrhage	0 (0%)	1 (0.1%)	0.99
<b>Hematologic/ Lymphatic</b>	6 (0.4%)	0 (0%)	0.031
Petechiae	1 (0.1%)	0 (0%)	0.99
Thrombocytopenia	5 (0.3%)	0 (0%)	0.062
<b>Nervous system</b>	1 (0.1%)	4 (0.2%)	0.38
Confusion	0 (0%)	3 (0.2%)	0.25
<b>Respiratory system</b>	3 (0.2%)	2 (0.1%)	0.99
Epistaxis	2 (0.1%)	1 (0.1%)	0.99
Hemoptysis	1 (0.1%)	0 (0.1%)	0.99
<b>Urogenital system</b>	3 (0.2%)	3 (0.2%)	0.99
Dysfunctional uterine bleeding	1 (0.1%)	0 (0%)	0.99
Hematuria	2 (0.1%)	3 (0.2%)	0.99

a. Data from NDA volume 1.48, reference 9, tables 35.

b. p value calculated using chi square test by the sponsor.

The sponsor also collected the laboratory AEs during the trial, including those leading to discontinuation. As summarized below, more subjects in the tirofiban group had a laboratory AE and had a drug-related lab AE than the subjects in the heparin group. This increase was primarily due to increased incidence of two labs in the tirofiban group: thrombocytopenia (2.0% vs. 0.9% in the heparin group, n=0.013); and increased hematuria (8.7% vs. 6.2% in the heparin group, p=0.008).

Table 6.2.2.13.2.3 Laboratory AEs, including AEs leading to discontinuation, in the PRISM trial<sup>a</sup>.

	Tirofiban alone n=1616	Heparin alone n=1616	p value <sup>b</sup>
<b>With any laboratory AE</b>	346 (21.4%)	297 (18.4%)	0.034
<b>With drug-related laboratory AE<sup>c</sup></b>	79 (4.9%)	41 (2.5%)	0.001
<b>With any serious laboratory AE</b>	8 (0.5%)	4 (0.2%)	0.39
<b>With serious drug-related laboratory AE</b>	4 (0.2%)	0 (0%)	0.12
<b>Discontinued due to a laboratory AE</b>	8 (0.5%)	5 (0.3%)	0.58
<b>Discontinued due to bleeding lab AE</b>	1 (0.1%)	4 (0.2%)	0.37

a. Data from NDA volume 1.48, reference 9, tables 36.

b. p value calculated using chi square test.

c. Drug-related per individual investigator.

### 6.2.2.13.2 Comments on Specific Safety Parameters (cont)

#### Bleeding AEs

Per the sponsor, the bleeding was ‘considerably more frequent in the tirofiban group.’

There was no significant difference in the % of subjects who had at least one episode of major bleeding, both by site and as judged by the TIMI classification. Protocol-specified major bleeds occurred in 21 (1.3%)% of the tirofiban and 14 (0.9%) of the heparin groups (p=0.31). TIMI-class major bleeds occurred in 0.4% of the tirofiban and 0.4% of the heparin groups (p=0.91).

Table 6.2.2.13.2.4 Major bleeding AEs in the PRISM trial<sup>a</sup>.

	Tirofiban n=1616	Heparin n=1616	p value T vs. H <sup>b</sup>
<b>Major Bleeding (protocol defined)<sup>c</sup></b>			
<b>Yes</b>	21 (1.3%)	14 (0.9%)	0.31
<b>TIMI Bleeding</b>			0.91
<b>Major</b>	7 (0.4%)	6 (0.4%)	
<b>Minor</b>	33 (2.0%)	31 (1.9%)	
<b>Loss/ No site identified</b>	3 (0.2%)	4 (0.2%)	

a. Data from NDA vol. 1.48, ref 9, table 40 and electronic datasets.

b. p value calculated using chi square test.

c. Major bleeding defined as bleeding resulting in: hemoglobin drop >5 g/dl; transfusion of 2 units or more; corrective surgery; intracranial hemorrhage; or retroperitoneal hemorrhage.

The incidence of moderate, severe and life-threatening bleeding are shown below grouped by site of bleeding. There was a significant increase in the incidence of bleeding in the tirofiban group at the following sites: oral; nasal; GU; GI; pulmonary (hemoptysis); other; and unknown. Life-threatening bleeds occurred at a similar frequency in the two groups (0.6 vs. 0.4%). Note, however, the increased frequency of moderate, severe, and life-threatening bleeding the GI category for the tirofiban group.

Two subjects in both groups (0.1%) had intracranial bleeds, and one subject in the tirofiban group had a life-threatening retroperitoneal bleed. Classified under the ‘other’ category were two episodes of pericardial/mediastinal bleeding in the tirofiban group (AN 2545, and 5597), and one in the heparin group (AN 2467).

Table 6.2.2.13.2.5 Major bleeding AEs in the PRISM trial<sup>a</sup>.

	Tirofiban n=1616	Heparin n=1616	p-value
<b>Any site</b>			<0.001
Oozing	205 (12.7%)	134 (8.3%)	
Mild	151 (9.3%)	98 (6.1%)	
Moderate	33 (2.0%)	27 (1.7%)	
Severe	17 (1.1%)	13 (0.8%)	
Life-threatening	10 (0.6%)	7 (0.4%)	
<b>IV site</b>			0.048
Oozing	41 (2.5%)	25 (1.5%)	
Mild	25 (1.5%)	18 (1.1%)	
Moderate	2 (0.1%)	3 (0.2%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	1 (0.1%)	
<b>Catheter site</b>			0.71
Oozing	16 (1.0%)	16 (1.0%)	
Mild	7 (0.4%)	9 (0.6%)	
Moderate	5 (0.3%)	6 (0.4%)	
Severe	4 (0.2%)	3 (0.2%)	
Life-threatening	0 (0%)	1 (0.1%)	

6.2.2.13.2 Comments on Specific Safety Parameters (cont)

Bleeding AEs (cont)

Table 6.2.2.13.2.5 Major bleeding AEs in the PRISM trial (cont)<sup>a</sup>

	Tirofiban n=1616	Heparin n=1616	p-value
<b>Oral</b>			0.018
Oozing	9 (0.6%)	1 (0.1%)	
Mild	4 (0.2%)	2 (0.1%)	
Moderate	1 (0.1%)	1 (0.1%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>Nasal</b>			<0.001
Oozing	48 (5.3%)	10 (0.6%)	
Mild	33 (3%)	5 (0.3%)	
Moderate	2 (0.1%)	1 (0.1%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>GU/ Hematuria</b>			0.004
Oozing	84 (90.3%)	65 (4.0%)	
Mild	63 (5.3%)	38 (2.4%)	
Moderate	7 (0.4%)	7 (0.4%)	
Severe	1 (0.1%)	1 (0.1%)	
Life-threatening	0 (0%)	0 (0%)	
<b>GI</b>			0.002
Oozing	36 (2.2%)	27 (1.7%)	
Mild	28 (1.7%)	14 (0.9%)	
Moderate	9 (0.6%)	3 (0.2%)	
Severe	5 (0.3%)	3 (0.2%)	
Life-threatening	3 (0.2%)	0 (0%)	
<b>Hemoptysis</b>			0.032
Oozing	4 (0.2%)	1 (0.1%)	
Mild	6 (0.4%)	2 (0.2%)	
Moderate	1 (0.1%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>Intracranial</b>			0.99
Oozing	1 (0.1%)	0 (0%)	
Mild	1 (0.1%)	0 (0%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	2 (0.1%)	
<b>Retroperitoneal</b>			0.99
Oozing	0 (0%)	0 (0%)	
Mild	0 (0%)	0 (0%)	
Moderate	0 (0%)	1 (0.1%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	1 (0.1%)	0 (0%)	
<b>Other</b>			0.011
Oozing	15 (0.9%)	5 (0.3%)	
Mild	8 (0.5%)	4 (0.2%)	
Moderate	4 (0.2%)	4 (0.2%)	
Severe	5 (0.3%)	2 (0.1%)	
Life-threatening	6 (0.4%)	4 (0.2%)	

a. Data from NDA vol. 1.48, ref 9, table 43.

b. p value calculated using chi square test

**6.2.2.13.2 Comments on Specific Safety Parameters (cont)**  
**Bleeding AEs (cont)**

**Transfusions in the PRISM trial**

More subjects in the tirofiban group (2.4%) than in the heparin group (1.4%) required a transfusion, although this difference was not statistically significant (p=0.070). Similarly, subjects in the tirofiban group required on average more units of packed red blood cells (0.066 units per subject) than subjects in the heparin group (0.056 units per subject), a difference that was also not statistically significant (p=0.12).

Table 6.2.2.13.2.6 Percent of subjects requiring transfusions-in the PRISM trial<sup>a</sup>.

	<b>Tirofiban (N=1616)</b>	<b>Heparin (N=1616)</b>	<b>p value T vs. H</b>
<b>Type</b>	n	n	p-value
<b>Any Transfusion</b>			0.070
No	1578 (97.6%)	1593 (98.6%)	
Yes	38 (2.4%)	23 (1.4%)	
<b>Whole Blood</b>			0.69
No	1612 (99.8%)	1614 (99.9%)	
Yes	4 (0.2%)	2 (0.1%)	
<b>FFP</b>			0.55
No	1609 (99.6%)	1612 (99.8%)	
Yes	7 (0.4%)	4 (0.2%)	
<b>PRBC</b>			0.16
No	1585 (98.1%)	1596 (98.8%)	
Yes	31 (1.9%)	20 (1.2%)	
<b>Cryoprecipitates</b>			0.99
No	1615 (99.9%)	1616 (100%)	
Yes	1 (0.1%)	0 (0.0%)	
<b>Platelets</b>			0.18
No	1606 (99.4%)	1612 (99.8%)	
Yes	10 (0.6%)	4 (0.2%)	
<b>Other</b>			0.62
No	1613 (99.8%)	1615 (99.9%)	
Yes	3 (0.2%)	1 (0.1%)	

a. Data from sponsor at request of medical reviewer.

6.2.2.13.2 Comments on Specific Safety Parameters (cont)  
Bleeding AEs (cont)

Table 6.2.2.13.2.7 Number of PRBC units transfused per subject in the PRISM trial.

Type of transfusion n (%)	Tirofiban (N=1616)	Heparin(N=1616)	p-value
<b>Whole Blood</b>			
0	1612 (99.8%)	1614 (99.9%)	
1	1 (0.1%)	1 (0.1%)	
2	1 (0.1%)	1 (0.1%)	
3	1 (0.1%)	0 (0.0%)	
4	1 (0.1%)	0 (0.1%)	
Mean (s.d.)	.006 (.136)	.002 (.056)	0.41
<b>FFP</b>			
0	1609 (99.6%)	1612 (99.8%)	
1	1 (0.1%)	0 (0.0%)	
2	2 (0.1%)	1 (0.1%)	
4 or more	4 (0.2%)	3 (0.2%)	
Mean	.015 (.273)	.021 (.504)	0.37
<b>PRBC</b>			
0	1585 (98.1%)	1596 (98.8%)	
1	6 (0.4%)	1 (0.1%)	
2	11 (0.7%)	10 (0.6%)	
3	4 (0.2%)	3 (0.2%)	
4 or more	10 (0.6%)	6 (0.4%)	
Mean	.066 (.648)	.056 (.084)	0.12
<b>Platelets</b>			
0	1606 (99.4%)	1612 (99.8%)	
1	1 (0.1%)	1 (0.1%)	
2	1 (0.1%)	0 (0.0%)	
3	1 (0.1%)	0 (0.0%)	
4 or more	7 (0.4%)	3 (0.2%)	
Mean	.031 (.431)	.028 (.713)	0.11

a. Data from sponsor at request of medical reviewer.

Thrombocytopenia

Low absolute platelet counts were more common in the tirofiban group than in the heparin group, regardless of the level used to detect thrombocytopenia. Seventeen (1.1%) of the tirofiban group had at least one platelet count  $<90,000/\text{mm}^3$ , compared with 7 (0.4%) of the heparin group ( $p=0.042$ ). Of the seventeen subjects in the tirofiban group, 5 were discontinued from study drug, compared with 1/5 of the heparin subjects. One other tirofiban subject and three heparin subjects had platelet counts  $<90,000/\text{mm}^3$  which were not counted as AEs by the investigators. From subjects with an available pre- and post-treatment platelet count, the tirofiban group also had a higher incidence of thrombocytopenia (shown below).

Table 6.2.2.13.2.8 Incidence of clinical AEs reported by investigators as decreased platelet counts in PRISM.

Lab adverse event	Tirofiban alone n=1616	Heparin alone n=1616	p value
Platelet count decrease to $<100,000/\text{mm}^3$	22 (1.4%)	11 (0.7%)	0.056
Platelet count decrease to $<90,000/\text{mm}^3$	16 (1.0%)	5 (0.3%)	0.016
Platelet count decrease to $<50,000/\text{mm}^3$	5 (0.3%)	0 (0%)	0.031
Platelet count decrease to $<20,000/\text{mm}^3$	3 (0.2%)	1 (0.1%)	$>0.05$

a. Data from NDA volume 1.48, ref. 9, appendix 4.1.26.

Thrombocytopenia was associated with bleeding complications in five tirofiban subjects and in 3 heparin subjects, listed below. The clinical consequences of thrombocytopenia will be discussed further in sections 8.1 and 8.2.

**6.2.2.13.2 Comments on Specific Safety Parameters (cont)**  
**Bleeding AEs (cont)**

Table 6.2.2.13.2.9 Subjects with thrombocytopenia and other bleeding AEs in the PRISM trial<sup>a</sup>.

Subject #	Pre-study/nadir Platelet # (/mm <sup>3</sup> )	Hour of AE	AEs
<b>Tirofiban</b>			
AN 1462	172,000/ 19,000	17.5	Thrombocytopenia Epistaxis
AN 4919	181,000/ 6,000	24	Thrombocytopenia Ecchymoses, IV site Epistaxis
AN 4557	201,000/ 64,000	Day 4	Thrombocytopenia Epistaxis
AN 1985	174,000/ <b>85,000</b>	12	Thrombocytopenia GI bleeding
AN 3494	242,000/ <b>53,000</b>	>99	Post-op bleeding
<b>Heparin</b>			
AN 2352 <sup>b</sup>	176,000/ 9,000	63.8	Thrombocytopenia Post-op bleeding
AN 1801	159,000/ 68,000	70	Thrombocytopenia Post-op bleeding
AN 2373	206,000/ <b>58,000</b>	>99	Thrombocytopenia Post-op bleeding

a. Data from NDA volume 1.48, rer 9, tables 51 and 52

b. This individual did not have thrombocytopenia or low platelet count identified as an adverse event by the primary investigator.

c. This individual also received Reopro and developed chills shortly thereafter. The investigator felt that the Reopro was a more likely cause of the thrombocytopenia.

**6.2.2.14 PRISM Efficacy Summary**

The two groups of subjects in the PRISM trial were well-balanced as regards demographics and clinical presentation at time of entry into the trial (see tables 6.2.2.12.1.1 to 6.2.2.12.1.3, p. 112). The groups were also well-balanced with regard to duration of study drug therapy (see section 6.2.2.12.2c.2, p. 115). The heparin group was given a larger number of heparin boluses (see table 6.2.1.12.2c.3), and had a higher aPTT (as would be expected, see table 6.2.1.12.2c.4, p. 116). The two groups were otherwise matched **with** regard to concomitant medications.

1. In the PRISM trial, the use of tirofiban alone was associated with a significant decrease in the incidence of refractory ischemic conditions (RIC), MI and death at the end of 48 hours, when compared with heparin (the pre-specified primary endpoint). Through 48 hours, 61/1616 (3.8%) in the tirofiban group and 91/1616 (5.6%) in the heparin group met the primary endpoint. This difference between treatments has an odds ratio of 0.659, which represents a 33% risk reduction for an event in the tirofiban group (p=0.014) (see table 6.2.2.12.2d.1, p. 117).

The incidence of the combined endpoint was non-significantly decreased at the end of 7 and 30 days in the tirofiban group compared with heparin (see table 6.2.2.12.2d.1, p. 117).

Of the three components of the primary endpoint, only RIC was significantly reduced at the end of 48 hours in the tirofiban group. In a somewhat surprising result, death at the end of 30 days was also significantly reduced in the tirofiban arm compared with heparin: tirofiban, 37 (2.3%); versus heparin 59 (3.6%), p=0.021.

2. Based on exploratory and post-hoc analyses performed by the sponsor, there was no significant effect of tirofiban to reduce either the number or severity of angina episodes during the hospitalization. There was also no significant effect of tirofiban to reduce the number or types or cardiac procedures undergone during the initial hospitalization (see table 6.2.2.12.3.4, p. 120).

3. Based on pre-specified subgroup analyses, tirofiban had a consistent, small, effect to reduce the incidence of the combined RI/MI/Death endpoint in many subject populations (see table 6.2.2.12.3.6, p. 122).

4. The sponsor performed a post-hoc analysis of the clinical events in subjects who underwent PTCA (a population somewhat analogous to the RESTORE trial population). In this small subgroup, there were a numerically lower incidence of RIC/MI/Death in the tirofiban arm (see table 6.2.2.12.3.5). In addition, the sponsor analyzed the incidence of the primary endpoint in subjects who did not receive PTCA during the trial. There was little difference between the tirofiban and heparin groups in this analysis (14.4% vs. 14.2%, see table 6.2.2.12.3.5, p. 121).

5. The pharmacokinetics of tirofiban alone were also examined in a subgroup of the tirofiban arm. There was a significant correlation between the calculated creatinine clearance and plasma tirofiban clearance (see table 6.2.2.12.3.8, p. 123). In the subjects with creatinine clearances <30 ml/min, the estimated tirofiban clearance was reduced by 52%.

#### 6.2.2.15 PRISM Safety Summary

The safety database of PRISM will be integrated with the other phase II-III studies and discussed in **the** integrated safety summary, sections 8.0-8.2. The comments below are based on the data presented above.

1. No adverse effect of tirofiban on the incidence of death up to 30 days after the start of the study was detected. There was a trend, which achieved statistical significance by 30 days, towards a lower death rate in the tirofiban group, compared with heparin. Of the deaths, summarized in section 8.1.1.1 e, the majority were related to progression of underlying disease processes, and none were due to unusual or unexpected toxicities of the study **drug** (tirofiban or heparin).

2. There were more discontinuations due to adverse events (AEs) in the tirofiban arm, as well as more discontinuations due to bleeding AEs (see tables 6.2.2.13.2.2 and 6.2.2.13.2.3, p. 125).

3. The incidence of major bleeding was similar in both group (see table 6.2.2.13.2.4, p. 126). There was, however, a significant increase in the incidence of bleeding adverse events in the tirofiban group at the following sites: oral; nasal; GU; GI; pulmonary (**hemoptysis**); other; and unknown. Life-threatening bleeds occurred at a similar frequency in the two groups (0.6 vs. 0.4%). There was an increased frequency of moderate, severe, and life-threatening bleeding the GI category for the **tirofiban** group. Two subjects in both groups (0.1%) had intracranial bleeds, and one subject in the **tirofiban** group had a life-threatening retroperitoneal bleed.

4. The subjects in the tirofiban group had a higher incidence rate of transfusion than the heparin group (2.4% vs. 1.4%,  $p=0.070$ , p. 128).

5. The incidence of thrombocytopenia was increased in the tirofiban group, compared with the heparin group (see table 6.2.2.13.2.8). There were no deaths caused by bleeding in either group, but more subjects in the tirofiban group had associated clinical events in conjunction with thrombocytopenia (see table 6.2.2.13.2.7, p. 129).

6. No unexpected toxicities of tirofiban were identified by this reviewer from the PRISM database.

### 6.2.3 Review of RESTORE Trial

#### 6.2.3.1 Title of Study

A randomized, double-blind, placebo-controlled study of the effects of tirofiban (MK-0383) on cardiac outcomes in subjects undergoing percutaneous transluminal coronary angioplasty or atherectomy due to unstable angina pectoris or following acute myocardial infarction. RESTORE (protocol 013).

#### 6.2.3.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 1.37, Table A-1 (pages A-6 to A-101).

The RESTORE trial was conducted at 111 sites, 96 sites in the United States and 15 outside the United States.

#### 6.2.3.3 Background

Initial Protocol: submitted 10.25.94

First protocol amendment: submitted 11.30.94

1. modified inclusion criteria slightly;
2. modified the study design, adding a safety analysis after the first 200 subjects, allowing a reduction in the rate of tirofiban infusion from 0.15 µg/kg/min to 0.10 µg/kg/min for 36 hours if there is excess bleeding in the tirofiban group;
3. modified the study design, stratifying the subjects according to whether the PTCA/atherectomy was 'primary' (done for therapy of MI instead of thrombolysis within 12 hours of onset of pain) or 'secondary' PTCA/atherectomy;
4. provided guidelines for heparin dosing based on subject weight and activated clotting time results; and
5. called for heparin discontinuation after the PTCA/ atherectomy if medically feasible.

Second protocol amendment: submitted 10.16.95

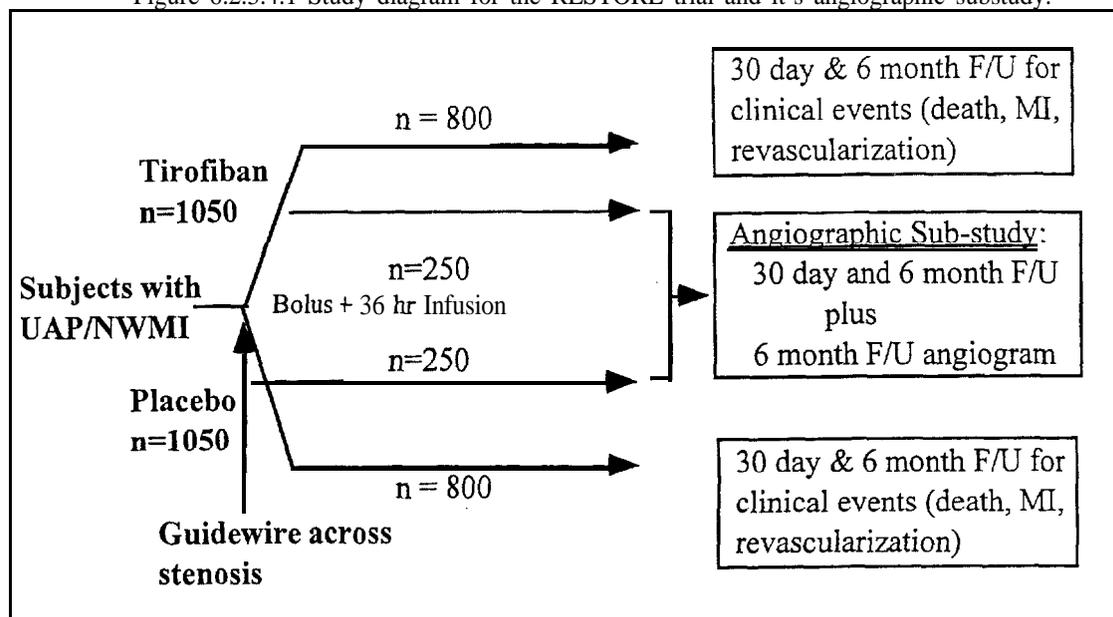
1. provided more specific endpoint definitions, including the timing of onset of anginal pain;
2. slightly modified exclusion criteria, adding an exclusion for female subjects without a negative pregnancy screen, for subjects with >50% LAD lesion unprotected by grafts, and for subjects who are likely to require a stent placement as part of a staged procedure;
3. provided more detailed instructions for study drug initiation;
4. provided more detailed instructions for study drug discontinuation, including discontinuation for use of dextran, warfarin, or ticlopidine, or an unexplained decrease in hemoglobin;
5. provided detailed procedures for the angiographic substudy and catheterization laboratory validation for the substudy;
6. modified the data analysis section to exclude from the efficacy analysis subjects who were randomized but who never received study drug due to an administrative or technical reason; and
7. provided definitions for major and minor bleeding.

First drug shipment: 12.94

First subject entry: 1.95

### 6.2.3.4 Study Design

Figure 6.2.3.4.1 Study diagram for the RESTORE trial and its angiographic substudy.



#### General and Baseline

This was a randomized, double-blind, placebo-controlled, multicenter, multinational study. It was designed to investigate the safety, tolerability and effects of tirofiban on subsequent cardiac events when used in combination with heparin and aspirin in subjects undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy within 72 hours of presentation with an acute coronary ischemic syndrome (unstable angina pectoris or acute myocardial infarction, including both Q-wave and NQWMI). Subjects were randomly assigned to either tirofiban or placebo for 36 hours. All subjects also received open-label heparin (dosage and administration determined by the investigator with protocol guidelines) and open-label aspirin.

The primary endpoint of the trial was the incidence of the following events: death from any cause, nonfatal myocardial infarction, CABG, repeat percutaneous intervention for recurrent ischemia, or insertion of a coronary endovascular stent because of procedural failure within 30 days of original PTCA or atherectomy.

A subset of investigators was pre-selected by the sponsor to participate in an angiographic substudy involving approximately 500 of the subjects in the RESTORE trial. These subjects were treated exactly the same as all other subjects, except that they underwent a coronary angiogram for quantitative analysis of lumen diameter approximately 6 months after the PTCA/ atherectomy.

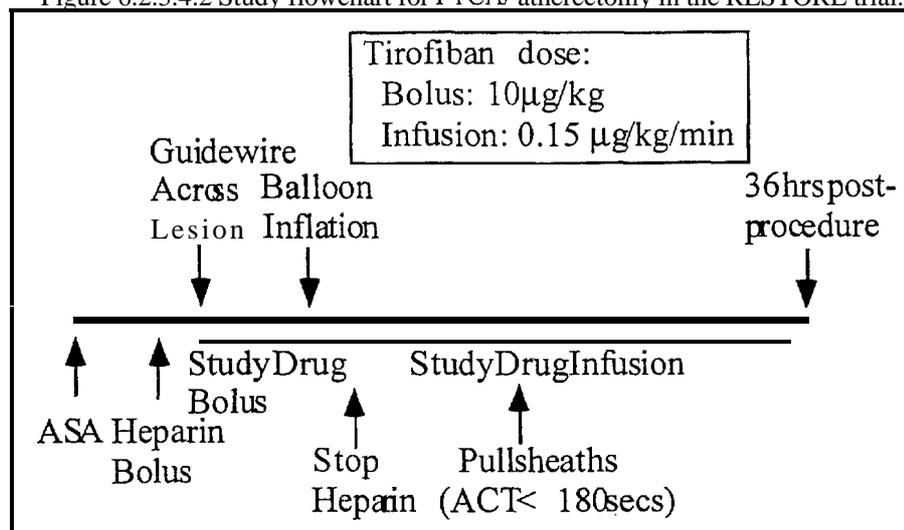
The study was conducted under the oversight of a Steering Committee, and in conjunction with a Data & Safety Monitoring Committee (DSMC). The Steering Committee was comprised of investigators, and was kept blinded to treatment groups for the duration of the study. The DSMC was appointed by the Steering Committee, was comprised of noninvestigators, and was unblinded to the treatment groups. The DSMC received monthly reports of adverse experience and endpoint data from the unblinded sponsor's statistician, and was responsible for the 200-subject safety analysis and the two interim analyses. All other sponsor and study personnel were blinded for the duration of the study. An Endpoint Committee was appointed by the Steering Committee for the purpose of endpoint adjudication. The Endpoint Committee was comprised of investigators, and was blinded for the duration of the study. At least two Endpoint Committee members had to agree on each adjudication; in the event of a tie decision, the case was sent to an additional Endpoint Committee member for a tie-breaking decision. The Endpoint Committee's adjudication was the final and binding determination as to whether or not events were considered endpoints for purposes of the efficacy analysis.

#### 6.2.3.4 Study Design (cont)

##### PTCA/ Atherectomy

Following entry into the study and randomization, the subjects underwent PTCA/ atherectomy as summarized in the figure below.

Figure 6.2.3.4.2 Study flowchart for PTCA/ atherectomy in the RESTORE trial.



The PTCA or atherectomy was performed according to institutional guidelines and standards. The heparin dosing was prepared and administered according to the catheterization laboratory's standard procedure but the investigator was asked to adhere to specified heparin-dosing guidelines if possible, at his/her discretion. These guidelines were as follows: The bolus of heparin prior to the procedure was to be 10,000 U for subjects weighing 70 kg or more; subjects <70 kg were to receive a weight-adjusted heparin bolus of 150 U/kg; the dosage could be decreased at the physician's discretion if the subject already had been anticoagulated; heparin was then to be administered as necessary to maintain ACT in the approximate range of 300 to 400 seconds during the procedure. During the PTCA/atherectomy procedure, as soon as the guidewire was across the lesion and the operator was ready to proceed with balloon inflation or activation of the atherectomy device, the study drug was administered as a bolus by syringe (not by pump) over 3 minutes. On completion of the bolus administration, balloon inflation or atherectomy device activation could proceed. The study drug infusion was started when the balloon inflation took place or when the atherectomy device was activated. The subject was to be observed at least 20 minutes after the final inflation to ensure stability prior to leaving the laboratory.

##### Following the PTCA/ Atherectomy

In general, heparin was to be discontinued at the conclusion of the PTCA/atherectomy procedure, and sheaths removed when ACT was <180 seconds. The study drug infusion was to continue while the sheath was being removed. If necessary, at the treating physician's discretion, heparin could be restarted either after sheath removal or after PTCA/atherectomy before sheath removal, for medical reasons such as: imperfect outcome of the procedure (e.g., large tear, intraluminal filling defect, or residual stenosis >40%), large thrombus load, continuing rest angina through the procedure, abrupt closure or very active artery during the procedure, or side branch occlusion. If heparin was restarted after PTCA/atherectomy but before sheath removal, an ACT <180 seconds was to be documented before sheath removal. If PTCA/atherectomy was performed using a femoral approach, the subject was to remain at bed rest overnight (or for at least 12 hours) following sheath removal. The subject could be ambulated after examination and clearance by the physician while the study drug infusion continued. If PTCA/atherectomy was performed using a nonfemoral approach, the subject could be ambulated at any time after the procedure at the physician's discretion. The study drug was to be infused for a total of 36 hours unless an intracoronary stent was placed. Because of the use of dextran, coumadin, and/or ticlopidine in stented subjects, the Steering Committee instructed that study drug be discontinued at the time of stent placement.

During the 36-hour period following study drug initiation, the subject was observed carefully for signs of bleeding. If at any time the platelet count dropped to <100,000/mm<sup>3</sup> or decreased to 60% of the predrug value, the test was to be repeated immediately. This platelet count was to be confirmed by redrawing blood in tubes that did not contain EDTA, and if the confirmed platelet count decreased to <90,000/mm<sup>3</sup> the infusion of study drug and heparin was to be discontinued. Aspirin, 325 mg orally, was to be administered 24 hours after the pre-procedure dose and then daily thereafter.

#### 6.2.3.4 Study Design (cont)

##### Angiographic substudy

A subset of the investigators participating in the trial were selected by the sponsor to participate in a substudy to investigate the effects of tirofiban vs. placebo on restenosis following PTCA or atherectomy. Patients at the selected sites were assigned randomly to receive tirofiban or placebo in a double-blind manner, and were studied identically to those in the primary study, except that subjects in the angiographic substudy underwent a coronary angiogram for quantitative analysis of lumen diameter approximately 6 months after the PTCA/atherectomy.

##### Reading of angiograms and clinical lab testing

All angiograms were read at the clinical sites as well as at a blinded angiographic core laboratory. The site investigator was asked to identify the 'culprit lesion.' At the core angiographic lab, all angiograms were reviewed by two blinded experienced angiographers, using ECGs and angiograms to identify the culprit lesion, rated as probably, possible or undetermined. The Steering Committee decided to exclude from analysis all angiograms performed  $\geq 97$  hours after randomization. This was done because they felt the angiograms were too remote from the treatment period.

All lab testing for routine chemistries and hematologies were performed at the individual centers. Special labs, such as tirofiban levels, were submitted to a central lab for analysis.

#### 6.2.3.5 Primary and Secondary Endpoints

##### Primary endpoint

1. The incidence of the following composite endpoint during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure.

##### Secondary endpoint

1. The incidence of the following composite endpoint during the first 6 months: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure.

##### Miscellaneous and post-hoc endpoints

1. The incidence of any one of the following endpoints during 30 days and 6 months of follow-up: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular *stent* because of procedural failure.

2. The degree of restenosis at 6 months of follow-up in subjects undergoing PTCA or atherectomy (performed on a subset of the subjects entered into RESTORE).

3. The incidence of emergency revascularization in the 30 days post-procedure (rather than any revascularization for recurrent ischemia).

##### Definitions of clinical endpoints used in the RESTORE trial

###### 1) Death

Death, due to any cause.

###### 2) Progression to Myocardial Infarction

a) In subjects entering the study with unstable angina and normal CWCK-MB at screening, without a history of myocardial infarction (MI) within 72 hours prior to randomization, the development of a new MI after completion of PTCA/ atherectomy and before hospital discharge was defined as:

(1) Typical chest pain with new ST-T changes or new pathologic Q waves (20.04 seconds in duration or with a depth above one quarter of the corresponding R wave amplitude in two or more contiguous leads) and an elevated CK-MB (or a serum CK more than twice the upper limit of normal if CK-MB is not available); OR

(2) A CK-MB 23 times the upper limit of normal, or CK  $\geq 3$  times the upper limit of normal with an elevated CK-MB, unaccompanied by chest pain and/or ECG changes.

b) In subjects entering the study within 72 hours following an acute MI (including subjects undergoing primary PTCA/ atherectomy), the development of a new MI after PTCA/ atherectomy and before hospital discharge was defined as:

(1) A CK-MB (or CK if CK-MB was not available) 23 times the upper limit of normal and representing an increase of  $\geq 33\%$  from the previous valley (defined as a decrease of at least 25% from a previous peak value but remaining at least twice the upper limit of normal); or

### 6.2.3.5 Primary and Secondary Endpoints (cont)

#### 2) Progression to Myocardial Infarction (cont)

(2) A CK-MB (or CK if CK-MB was not available)  $\geq 3$  times the upper limit of normal and representing an increase of 2100% from the previous value that is  $< 50\%$  of peak value and less than twice the upper limit of normal.

c) In all subjects, the development of a new MI after PTCA/ atherectomy and after hospital discharge was defined as:

(1) Typical chest pain with new ST-T changes or new pathologic Q waves (20.04 seconds in duration or with a depth above one quarter of the corresponding R wave amplitude in two or more contiguous leads) and an elevated CK-MB (or a serum CK more than twice the upper limit of normal if CK-MB is not available); OR

(2) A CK-MB  $\geq 2$  times the upper limit of normal, or CK  $\geq 2$  times the upper limit of normal with an elevated CK-MB, unaccompanied by chest pain and/or ECG changes.

d) In the case of an MI that occurred in association with a coronary artery bypass grafting procedure, the development of a new Q-wave was required as evidence of an MI but other evidence could also be considered by the Endpoint Committee.

#### 3) Coronary Artery Bypass Grafting (CABG)

CABG performed due to complication (e.g., large dissection, perforation) or failure (see definition below) of the initial PTCA/ atherectomy attempt, or due to recurrent ischemia following completion of the initial PTCA/ atherectomy. A post hoc analysis of subjects undergoing emergency CABG of any vessel (as adjudicated by the Endpoint Committee) within 30 days post-procedure was also performed.

#### 4) Repeat Percutaneous Intervention for Recurrent **Ischemia**

Subsequent revascularization (i.e., **after** completion of the initial PTCA/ atherectomy) of the same vessel dilated at the initial procedure, including PTCA/ atherectomy and intracoronary stent insertion for recurrent ischemia. A post hoc analysis of subjects undergoing emergency coronary revascularization of any vessel (as adjudicated by the Endpoint Committee) within 30 days post-procedure was also performed.

#### 5) Insertion of Intracoronary Stent Because of Procedure Failure

A stent placed immediately following an unsuccessful initial PTCA/ atherectomy attempt was considered an endpoint if there was imminent or complete abrupt closure prior to stent placement, as demonstrated by:

- a) TIMI (Thrombolysis in Myocardial Infarction Trial) grade 0 to 1 flow in the target vessel, or
- b) TIMI grade 2 flow in the target vessel associated with a local dissection or residual stenosis  $> 50\%$ .

Any PTCA, atherectomy, or stent placement performed after completion of the initial procedure was considered an endpoint.

### 6.2.3.6 Number of subjects/ randomization

Table 6.2.3.6.1 Patients enrolled in the RESTORE trial.

Tirofiban	Placebo
n=1071	n=1070

Based on the EPIC trial results, the true event rate in the placebo group of the RESTORE trial was assumed to be 12.8%. With 1050 subjects per treatment arm, this trial would have >90% power to detect a 35% reduction in the event rate in the tirofiban group, or approximately 80% power to detect a 30% reduction, at the 5% (2-sided) significance level. The final event rate in the placebo group at 30 days was 12.2%.

The study was to include 2100 subjects studied at approximately 100 centers. Subjects were randomly assigned, via a computer-generated allocation schedule, to either tirofiban (as a bolus of 10 µg/kg intravenously followed by an infusion of 0.15 µg/kg/min) or placebo for 36 hours.

A subset of the investigators participating in the trial were selected by the sponsor to participate in a substudy to investigate the effects of tirofiban vs. placebo on restenosis following PTCA/atherectomy. Patients at the selected sites were assigned randomly to receive tirofiban or placebo in a double-blind manner, and were studied identically to those in the primary study, except that subjects in the angiographic substudy underwent a follow-up coronary angiogram for quantitative analysis of lumen diameter approximately 6 months after the PTCA/atherectomy. A total of 211 subjects in the tirofiban group and 205 in the placebo group have two available angiograms as part of this sub-group.

### 6.2.3.7 Inclusion/ Exclusion Criteria

#### Inclusion Criteria

1) Subjects were to be of either sex, scheduled to undergo PTCA or atherectomy, with an approved device, for a coronary artery occlusion within 72 hours of clinical presentation (i.e., within 72 hours of last qualifying episode of chest pain) with an acute coronary ischemic syndrome, defined as:

a) Unstable angina, defined as any of the following:

(1) Episode of typical anginal pain occurring at rest or with minimal effort, associated with ECG changes suggestive of myocardial ischemia.

(2) Episode of typical anginal pain occurring at rest or with minimal effort, associated with hemodynamic changes suggestive of myocardial ischemia.

(3) Episode of typical anginal pain occurring at rest or with minimal effort, with angiographic evidence of thrombus in the target vessel immediately before PTCA or atherectomy (i.e., stenosis >70% plus any of the following: hazy appearance, intraluminal filling defect, overhanging edge with scalloped border, highly eccentric lesion, or reduced blood flow).

b) Acute myocardial infarction, defined as typical chest pain with ST-T changes or pathologic Q-waves (20.04 seconds in duration or with a depth greater than one quarter of the corresponding R-wave amplitude in two or more contiguous leads) and a serum creatine kinase more than twice the upper limit of normal, or a creatine kinase myocardial band >5%.

2) Subjects were to be above the age of consent and <85 years of age.

#### Exclusion Criteria

Subjects who fulfilled the above inclusion criteria but who manifested any of the following exclusion criteria at the time of randomization were not eligible for the study:

1) Pregnant or nursing women; women of childbearing potential must have had a negative pregnancy test prior to receiving study drug.

2) Thrombolytic therapy within 24 hours prior to the PTCA or atherectomy.

3) Presence of >50% left main lesion unprotected by bypass grafts.

4) Allergy or intolerance to aspirin or heparin (including heparin-induced thrombocytopenia).

5) History or symptoms (e.g., severe pain radiating to the back) suggestive of aortic dissection.

6) Subjects with uncontrolled severe cardiac arrhythmias or any subject requiring ongoing intravenous antiarrhythmic therapy prior to balloon angioplasty or atherectomy.

### 6.2.3.7 Inclusion/ Exclusion Criteria (cont)

#### Exclusion Criteria (cont)

- 7) Subjects with a contraindication to anticoagulation:
- a) Past or present bleeding disorder including a history of the following within 3 months prior to randomization: gastrointestinal bleeding, gross (visible) hematuria, or known presence of occult blood in the stool. Heparinized subject with more than “trace” or “small” (i.e., >20 cells/hpf) urine blood prior to the procedure. Any subject with a known platelet disorder or history of thrombocytopenia was excluded.
  - b) Any confirmed persistent recording of systolic blood pressure exceeding 180 mmHg and/or diastolic blood pressure exceeding 105 mmHg at time of enrollment.
  - c) Any history of stroke or other intracranial pathology at any time, or transient ischemic attack within 1 year.
  - d) Prolonged cardiopulmonary resuscitation within the 2 weeks prior to randomization.
  - e) Severe physical trauma within 1 month prior to randomization.
  - f) Major surgery or biopsy (noncutaneous) within 1 month prior to enrollment.
  - g) Active peptic ulcer disease within 3 months prior to randomization.
  - h) Probable pericarditis.
  - i) Presence of known significant retinopathy (i.e., hemorrhages or exudates).
- 8) History of recent or ongoing alcohol abuse or other drug abuse.
- 9) Subjects with acute pulmonary edema (rales present over more than 50% of the lung fields) or subjects with severe congestive heart failure (New York Heart Association Functional Class III or IV).
- 10) Sustained supine, sitting or standing systolic blood pressure <95 mmHg or evidence of cardiogenic shock at randomization.
- 11) Subjects with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.
- 12) Subjects with uncontrolled diabetes mellitus or other uncontrolled endocrinopathy.
- 13) Subjects with significant systemic, renal, pulmonary, hepatic, neurological or hematological disorders.
- 14) Subjects with clinically important abnormal laboratory findings including:
- a) Serum creatinine >2.0 mg/dL.
  - b) Hemoglobin <11 gm/dL or hematocrit <34%.
  - c) Platelet count <150,000/mm<sup>3</sup>.
  - d) Prothrombin time (PT) >1.3 times the laboratory control.
- 15) Subjects receiving another investigational drug within 4 weeks prior to randomization, or subject with any previous exposure to tirofiban.
- 16) Subjects with any other medical condition, which, in the investigator’s opinion, made survival for the duration of the study unlikely, or would otherwise have interfered with optimal participation in the study or produce a significant risk to the subject.
- 17) Subjects who was unable to give informed consent.
- 18) Subjects who was likely to undergo a staged procedure, or to require stent placement.
- 19) Subjects with a PTCA or atherectomy of a non-target vessel within 1 month of the study.
- 20) Subjects undergoing dilatation of a prior stent.
- 21) Subjects undergoing revascularization with a Rotablator or Tec device.

### 6.2.3.8 Dosage/ Administration

The three trials submitted in the NDA utilized three separate dosing regimens for tirofiban, as seen in the table below. See appendix 10, p. 370, for discussion of the tirofiban regimen used in each of the Phase III studies. When used in conjunction with heparin, the RESTORE trial used a higher rate of infusion of tirofiban than did PRISM-PLUS. This reflects the design of the RESTORE trial, which called for discontinuation of heparin following the PTCA/ angioplasty (see 6.2.3.4, p. 132).

The heparin dosing was prepared and administered according to the catheterization laboratory’s standard procedure but the investigator was asked to adhere to specified heparin-dosing guidelines if possible, at his/her discretion. These guidelines were as follows: The bolus of heparin prior to the procedure was to be 10,000 U for subjects weighing 70 kg or more; subjects <70 kg were to receive a weight-adjusted heparin bolus of 150 U/kg; the dosage could be decreased at the physician’s discretion if the subject already had been anticoagulated; heparin was then to be administered as necessary to maintain ACT in the approximate range of 300 to 400 seconds during the procedure. Heparin was then to be discontinued if possible shortly after completion of the procedure.

### 6.2.3.8 Dosage/ Administration (cont)

The three phase III trials submitted in the NDA utilized three separate dosing regimens for tirofiban, as seen in the table below.

Table 6.2.3.8.1 Dosing regimens used in the phase III tirofiban studies.

Trial	Design (arms)	Tirofiban Regimen	Heparin Regimen
PRISM	1. Tirofiban 2. Heparin	0.6 µg/kg/min loading dose (30 mins.) 0.15 µg/kg/min maintenance	5000 U bolus 1000 U/hr infusion with adjustment as needed
PRISM-PLUS	1. Tirofiban  2. Tirofiban +Heparin 3. Heparin	0.6 µg/kg/min loading dose (30 mins.) 0.15 µg/kg/min maintenance  0.4 µg/kg/min loading dose (30 mins.) 0.10 µg/kg/min maintenance	None  5000 U bolus 1000 U/hr infusion with adjustment as needed
RESTORE	1. Tirofiban (+Heparin) <sup>a</sup> 2. Placebo (+Heparin)	10 µg/kg loading dose (3 mins.) 0.15 µg/kg/min maintenance	10,000 U bolus (150 u/kg if subject <70 kg) No infusion after PTCA complete

a. Per protocol, all subjects in the RESTORE trial received open-label heparin during the angiography/PTCA.

### 6.2.3.9 Duration/ Adjustment of Therapy

An early safety analysis was performed to assess bleeding risk after 200 subjects completed study drug infusion. Based on the result of this analysis and using predefined guidelines, the Data and Safety Monitoring Committee (DSMC) recommended continuing the study without changing the dose of tirofiban.

Tirofiban (or placebo) infusion was to continue for a total of 36 hours, unless the subject underwent atherectomy. Due to concerns about the co-administration of tirofiban with coumadin, ticlopidine and/or dextran, the Steering Committee directed that the tirofiban be discontinued at the time of stent placement.

Heparin was to be discontinued in the tirofiban group soon after the PTCA/ atherectomy.

### 6.2.3.10 Safety and Efficacy Endpoint Measured

Table 6.2.3.10.1 Timetable for clinical observations and lab measurements in the RESTORE trial<sup>a</sup>.

	≤24 Pre-PTCA <sup>b</sup>	3 Minutes Pre-PTCA	During PTCA	Immediately Post-PTCA	6 Hours Post-PTCA	24 Hours Post-PTCA	End of Infusion (36 hours)
Informed consent	X						
Physical exam	X						X
History	X						
ECG	X						X
Labs	X						X
PT/aPTT	X						X
ASA	X					X	
Study Drug		Bolus	Infusion				
Heparin		Note c					
Monitor ACT							
Remove sheaths					X		
CBC					X	X	
Adverse event & endpoints				X	X	X	X <sup>d</sup>

a. Data from NDA volume 1.55, reference 11, table 1.

b. PTCA: percutaneous transluminal angioplasty. This includes those subjects who underwent atherectomy.

c. Heparin dosed per standard practice with protocol-specified guidelines. Heparin was to be discontinued if possible immediately after the procedure.

d. Subjects were followed by telephone or clinic visit at 30 days and 6 months for endpoints.

### 6.2.3.11 Statistical Considerations

#### General statistical considerations

The safety and efficacy analyses were based on the intention-to-treat principle, with one exception: subjects who were randomized but who never received study drug for an administrative or technical reason (e.g., PTCA not done because the guidewire or catheter could not cross the lesion, indication for angioplasty changed or disappeared) were not included in the efficacy or safety analyses. The number of these excluded subjects were tabulated. In addition, a per-protocol analysis for selected efficacy parameters was planned. Patients would have been excluded from these analyses for either of the following reasons:

a) Patient did not have the last episode of chest pain associated with an acute coronary ischemic syndrome within 72 hours of the PTCA/ atherectomy procedure (however, a subject could be included in the analysis if the procedure was within 76 hours of the last episode of pain provided the delay was due solely to scheduling problems in the catheterization lab, and was authorized by the sponsor prior to subject randomization).

Acute coronary ischemic syndrome was defined as one of the following:

(1) Unstable angina, as defined by an episode of typical anginal pain occurring at rest or with minimal effort, associated with one of the following:

(a) ECG changes suggestive of myocardial ischemia;

(b) hemodynamic changes suggestive of myocardial ischemia; or

(c) angiographic evidence of thrombus in the target vessel immediately before PTCA or atherectomy (i.e., stenosis >70% plus any of the following: hazy appearance, intraluminal filling defect, overhanging edge with scalloped border, highly eccentric lesion, or reduced TIM1 grade flow).

(2) Acute myocardial infarction as defined by typical chest pain with ST-T changes or pathologic Q-waves and serum creatine kinase more than twice the upper limit of normal, or an abnormally elevated creatine kinase myocardial band.

b) Patient was 285 years of age.

Since only 1 subject was known to have a last episode of chest pain more than 72 hours before his PTCA/ atherectomy procedure and none of the subjects was more than 85 years old, the per-protocol analyses as described would have been redundant. One subject (AN 5676) received study drug, but did not have a qualifying procedure. In order to include this subject in the primary efficacy analyses it was necessary to assign him a qualifying procedure, since the model included factors or covariates for type of procedure. Since PTCA was by far the most prevalent procedure, and it appears AN 5676 would have had a PTCA if a procedure had been performed, he was assigned to the PTCA group. This was done for purposes of the analysis of the composite endpoints only.

#### Analytical Methods

##### a) Efficacy statistical analysis

The primary efficacy variable, the combined incidence of stent placement for abrupt or threatened closure, repeat revascularization, myocardial infarction and death within 30 days of PTCA or atherectomy, was analyzed using logistic regression analysis. Any subject experiencing one or more of the above events within 30 days was counted as having a primary event. The statistical significance of the differences between treatment groups with respect to the composite endpoint and its components was assessed using a logistic regression analysis. The dependent variable was an indicator of whether or not the subject experienced the specific endpoint, and the independent variables were an indicator of treatment group, an indicator of the inclusion criteria and an indicator for the type of procedure, PTCA or atherectomy. There was no significant interaction between treatment group and either inclusion criteria or type of procedure. Odds ratios and p-values provided in the summary tables reflect the effect of treatment after adjusting for procedure type and inclusion criteria. The effects of procedure type and inclusion criteria on the endpoint are addressed in the subgroup analysis. In this review, all statistical analyses are by the sponsor unless otherwise specified.

The secondary endpoint was the combined incidence of stent placement for abrupt or threatened closure, repeat revascularization myocardial infarction, and death within 6 months of PTCA or atherectomy. This analysis was based on the same subject cohort as the primary analysis and also used logistics regression. The time course of the treatment effect was explored by Kaplan-Meier curves, and the difference between curves was assessed with a Cox regression model.

The results for the primary efficacy variables were examined within several subgroups, in order to explore whether or not the effect of tirofiban was consistent in a variety of groups of subjects. The effect of tirofiban may appear to differ between subgroups by chance alone. Therefore, the statistical significance of the differing effect of tirofiban among subgroups (treatment-by-factor interactions) was also analyzed. The statistical method for the subgroup analyses was the same as described above for the primary efficacy results, except that subgroup results for inclusion criteria do not include the corresponding inclusion criterion as an independent variable.

### 6.2.3.11 Statistical Considerations (cont)

#### a) Efficacy statistical analysis (cont)

The statistical method for the treatment-by-factor interactions was similar, except that indicators for inclusion criteria were not included in these models and the interaction test was a likelihood ratio test (that is,  $-2 \log$  order likelihoods for the models with and without the interaction terms were computed, and their difference was a chi-square statistic with degrees of freedom equal to the number of interaction indicators). Note that the study was not designed to detect statistically significant results within subgroups, and therefore the lack of a statistically significant result does not necessarily indicate the lack of a drug effect within that subgroup. Therefore, p-values for the effect of tirofiban within subgroups were not displayed. Treatment-by-factor interactions that were statistically significant at the 10% level were footnoted and discussed, but p-values for treatment-by-factor interactions were not otherwise displayed. The treatment groups were compared with respect to the number of subjects undergoing cardiac procedures at any time during the 30-day period of the trial other than what was required by protocol or procedures that constituted an endpoint. Statistical significance of the differences between treatment groups were assessed with Fisher's exact test. In order to investigate the similarity of the two treatment groups at baseline, the two groups were compared with respect to a variety of variables: demographics, subject history, prestudy therapy, prestudy physical examination, prestudy clinical evaluation, prestudy ECG, prestudy laboratory variables, and type of primary procedure performed.

The p-values for between-group comparisons were based on the following methods:

- 1) for dichotomous variables (e.g., gender), Fisher's exact test was used;
- 2) for categorical variables (e.g., race), Chi-square test was used;
- 3) for ordinal variables (e.g., number of vessels treated), Wilcoxon rank-sum test was used;
- 4) for continuous variables (e.g., laboratory variables): Wilcoxon rank-sum test was used;
- 5) the difference between the two treatment groups in the proportions of subjects with restenosis at 6 months follow-up in the angiographic substudy was examined using Fisher's exact test.

#### b) Safety statistical analysis

For safety analysis, statistical significance of the difference between groups was based on Fisher's exact test or Wilcoxon's rank test. In this review, all statistical results are per the sponsor's analysis, unless otherwise specified.

#### Interim analyses for RESTORE trial

An early safety analysis was performed to assess bleeding risk after 200 subjects completed drug infusion.

There were two formal interim analyses performed after approximately 1/3 and 2/3 of the subjects completed the 30-day follow-up period. The early stopping rule was based on the O'Brien-Fleming boundary, which resulted in a critical p-value of 0.00059 at the first interim analysis and 0.015 at the second interim analysis. The protocol specified the plan that if; at the time of the first interim analysis, the projected number of subjects that would experience a clinical endpoint by the end of the trial was considerably  $<222$ , the Steering Committee which was blinded to treatment groups may recommend an increase in the total sample size based on the pooled-group event rate with no input whatsoever from the unblinded DSMB. The trial was not stopped early and the sample size was not increased. Due to these interim analyses, the significance level at the final analysis was adjusted from 0.05 to 0.047.

## 6.2.3.12 Efficacy Outcomes

### 6.2.3.12.1 Subject Demographics & Baseline Characteristics

The demographics and baseline characteristics of the subjects in the RESTORE trial are summarized in the following tables. Note that both valvular heart disease and previous coronary angiography were more likely to occur in the placebo group.

Table 6.2.3.12.1.1 Demographics of the RESTORE trial<sup>a</sup>.

Demographic	Tirofiban (n=1071)	Placebo (n=1070)	p value
<b>Gender</b>			0.808
Female	294 (27.4%)	288 (26.9%)	
Male	777 (72.6%)	782 (73.1%)	
<b>Race</b>			0.146
White	943 (88.1%)	962 (89.9%)	
Black	70 (6.5%)	50 (4.7%)	
Asian	7 (0.7%)	9 (0.8%)	
Hispanic	42 (3.9%)	33 (3.1%)	
Other	9 (0.8%)	16 (1.5%)	
<b>Common Diagnoses</b>			
Hypertension	575 (53.7%)	598 (55.9%)	0.318
Hypercholesterolemia	537 (50.1%)	525 (49.1%)	0.635
Family Hx of heart disease	559 (52.2%)	558 (52.1%)	1.000
Diabetes	210 (19.6%)	210 (19.6%)	1.000
Current Smoker	683 (63.8%)	714 (66.7%)	0.159
Valvular heart disease	28 (2.6%)	44 (4.1%)	0.056
Prior coronary angiography	322 (30.1%)	367 (34.3%)	0.037
Prior CABG	68 (6.3%)	86 (8.0%)	0.133
Prior PTCA	223 (20.8%)	213 (19.9%)	0.629
Prior UAP	941 (87.9%)	933 (87.2%)	0.648
Prior MI	378 (35.3%)	367 (34.3%)	0.650

- a. Data from NDA volume 1.55, tables 4-7, based on all randomized subjects, confirmed by FDA analysis.  
 b. Shaded diagnoses were nominally significantly different between the two groups by chi square analysis.

Table 6.2.3.12.1.2 Baseline physical exam findings in the RESTORE trial<sup>a</sup>.

Demographic	Tirofiban (n=1071)	Placebo (n=1070)	Combined (n=2141)
<b>Age (mean±sd)</b>	59.0±11.0	59.0±11.0	59.0±11.0
<b>Height (cm)</b>			
Males	N/A	N/A	
Females	N/A	N/A	
<b>Weight (kg)</b>			
Males	87.0±15.9	88.2±14.6	87.6±15.3
Females	73.9±18.3	76.7±14.5	73.3±16.5
<b>Supine BP</b>			
Systolic	127.8±19	127.7±20	
Diastolic	73.5±11.7	72.9±12.0	
<b>Pulse rate</b>	70.5±12.9	70.5±12.6	

- a. Data from NDA volume 1.55, tables 4-7, based on all randomized subjects, confirmed by FDA analysis

### 6.2.3.12.1 Subject Demographics & Baseline Characteristics (cont)

The two groups were well-matched in terms of the inclusion criteria used to enter the trial, as well as the extent of their coronary artery disease. The two groups were also well-balanced in terms of the drug therapies taken by the subjects prior to entry into the trial. There was no significant difference as regards any cardiovascular medications, with the exception of quinapril (tirofiban group, 5 (0.2%); placebo group, 22 (2.2%,  $p < 0.001$ ). There was no overall difference with regard to all ACE-inhibitors as a class, however.

Table 6.2.3.12.1.3 Inclusion criteria and extent of coronary artery disease at time of entry into the RESTORE trial<sup>a</sup>.

Demographic	Tirofiban (n=1071)	Placebo (n=1070)	p value
<b>Inclusion Criteria</b>			
<b>Procedure preceded by:</b>			<b>0.769</b>
Unstable angina	726 (67.8%)	728 (68.0%)	
Acute MI	274 (25.4%)	279 (26.1%)	
Acute MI (primary PTCA)	71 (6.6%)	63 (5.9%)	
<b>Extent of CAD</b>			0.449
Single-vessel	596 (55.7%)	617 (57.6%)	
Double-vessel	319 (29.8%)	284 (26.5%)	
Triple-vessel	131 (12.2%)	133 (12.4%)	
<b>Graft Stenosis</b>	20 (1.9%)	25 (2.3%)	0.547

a. Data from NDA volume 1.55, tables 8. Shown as n (%).

b. p values calculated using chi square.

### 6.2.3.12.2 Disposition of Subjects in the RESTORE trial

#### Disposition

The table below summarizes the disposition of the subjects enrolled in the RESTORE trial, including the reasons for subject discontinuation. Significantly more subjects in the tirofiban +heparin group were discontinued for AEs related to bleeding, and significantly more subjects in the heparin alone group were discontinued after meeting one of the clinical endpoints (death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure).

Table 6.2.3.12.2.4 Disposition of subjects randomized in the RESTORE trial<sup>a</sup>.

Patient Disposition	Tirofiban	Placebo	p value	Total
<b>Randomized</b>	1071	1070		2141
<b>Completed</b>	890 (83%)	880 (82%)		1770 (82.7%)
<b>Discontinued (total)</b>	181 (17%)	190 (18%)	0.608	371 (17.3%)
Presumed clinical endpoint	18 (1.7%)	39 (3.6%)	0.005	57 (2.7%)
Non-bleeding clinical AE <sup>b</sup>	24 (2.2%)	21 (2.0)	0.764	45 (2.1%)
Non-bleeding lab AE <sup>c</sup>	7 (0.7%)	1 (0.1%)	0.070	8 (0.4%)
Bleeding clinical or lab AE <sup>c</sup>	41 (3.8%)	13 (1.2%)	<0.001	54 (2.5%)
Stent usage	60 (5.6%)	76 (7.1%)	0.157	136 (6.4%)
Protocol-deviation	11 (1.0%)	13 (1.2%)	0.688	24 (1.1%)
Patient withdrew	5 (0.5%)	8 (0.8%)	0.422	13 (0.6%)
<b>Other reasons</b>	15 (1.4%)	19 (1.8%)	0.605	34 (1.6%)

a. Data from NDA volume 1.48, page 7037 and electronic datasets.

b. Includes subjects who discontinued due to nonbleeding clinical or nonbleeding laboratory adverse events.

c. Includes clinical or Laboratory discontinuations.

### 6.2.3.12.2 Disposition of Subjects in the RESTORE trial (cont)

#### Subject follow-up

The FDA also analyzed the extent of follow-up for subjects in each of the treatment groups, to gauge the adequacy of the clinical database. The following tables give descriptive statistics on length of follow-up for the patients who survived 30 days after randomization. The treatment groups were comparable with respect to the duration of follow-up, and >95% of the subjects had follow-up for at least 30 days.

Table 6 .3.12.2.2 Summary statistics on duration of follow-up in RESTORE".

	<b>Tirofiban +Heparin n=1062</b>	<b>Heparin n=1062</b>
<30 days	2.7%	3.6%
≥30 days	97.4%	96.4%
mean±sd	39±11	39±12
range	2-103	0-137
99th percentile	86	82
95th percentile	61	59
75th percentile	42	42
50th percentile	35	36
25th percentile	33	33
5th percentile	31	30
1st percentile	28	25

a. Data shown for 30 days survivors, collected from electronic datasets by FDA.

#### 6.2.3.12.2a Subject Selection

No information is available to this reviewer regarding the selection of subjects for this trial.

There were 71 patients in RESTORE who received an allocation number, but did not receive study drug due to an administrative or technical reason, and these patients were excluded from the analysis per the protocol amendment. The reasons these patients did not receive study drug were summarized in the table below.

Table 6.2.3.12.2a. I Reasons for exclusion from the RESTORE trial analysis<sup>a</sup>

<b>Reason for exclusion</b>	<b># of subjects</b>
No procedure performed	34
Unable to cross lesion	14
Physician changed treatment plan	8
Balloon pump required	3
Patient withdrew	3
Could not wait for study drug preparation	2
Pharmacy error	2
Discovered patient met an exclusion criterion	2
AE occurred/patient deteriorated	2
Patient required thrombolytics	

a. Data from sponsor at reviewer's request.

#### 6.2.3.12.2b Protocol Violations & Deviations

Subject AN 5676 received study drug, but had no qualifying procedure. It was determined that the would most likely have received a PTCA, and so was assigned to the PTCA group for analysis.

**6.2.3.12.2c Concomitant Therapies used after Trial Initiation**

The first table shows the initial procedures performed on the RESTORE subjects. The percentage of successful procedures (defined as <50% residual without need for intracoronary stent or emergency CABG) was higher in the tirofiban group than in the placebo group (92.1% vs. 89.5%, p=0.043). There were also more single-lesion treatments in the placebo group than in the tirofiban group (79.4% vs. 76.6%, p=0.054).

Table 6.2.3.12.2.1 Initial procedures performed on subjects in the RESTORE trial<sup>a</sup>

Procedure	Tirofiban (n=1071)	Placebo (n=1070)	pvalue
<b>PTCA</b>	<b>984 (92.0%)</b>	<b>995 (93.2%)</b>	<b>0.323</b>
<b>Atherectomy</b>	<b>86 (8.0%)</b>	<b>73 (6.8%)</b>	
<b>Sheath placement</b>			
Femoral	1039 (97.1%)	1041 (97.3%)	0.544
Brachial	5 (0.5%)	8 (0.8%)	
Other	26 (2.4%)	21 (2.0%)	
<b>Number of lesions treated</b>			
1	820 (76.6%)	850 (79.4%)	0.054
2	202 (18.9%)	186 (17.4%)	
3 or more	48 (4.5%)	34 (3.2%)	
<b>Number of vessels treated</b>			
1	974 (91.0%)	973 (90.9%)	0.885
2	94 (8.8%)	94 (8.8%)	
3 or more	2 (0.2%)	3 (0.3%)	
<b>Outcome</b>			
Successful	986 (92.1%)	958 (89.5%)	0.043
Unsuccessful	84 (7.9%)	112 (10.5%)	
<b>Nostent placement</b>	<b>990 (92.5)</b>	<b>975 (91.1%)</b>	<b>0.269</b>
<b>Stent placement</b>	<b>80 (7.5%)</b>	<b>95 (8.8%)</b>	

a. Data from NDA volume 1.55, tables 11. Shown as n (%).  
 b. p values calculated using chi square.

The duration of study drug administration was also compared between the placebo and tirofiban groups. No significant differences were detected.

Table 6.2.3.12.2.3 Duration of study drug administration in the RESTORE trial<sup>a</sup>

	Tirofiban (n=1071)	Placebo (n=1070)	p value
<b>Elapsed Time</b>			
<24 hrs	155 (14.5%)	173 (16.2%)	
≥24hrs	915 (85.5%)	895 (83.8%)	
≥32 hrs, 24 minutes (90% of 36 hrs)	887 (82.9%)	874 (81.8%)	
<b>Mean (SD) hrs</b>	<b>31.5±11.2</b>	<b>31.0±11.8</b>	<b>0.689</b>
<b>Median hrs</b>	<b>36.0</b>	<b>36.0</b>	

a. Data from NDA volume 1.55, tables 11. Shown as n (%).  
 b. p values calculated using chi square or t-test as appropriate.

Heparin was administered in open-label fashion during the RESTORE trial during the PTCA, and the results are summarized below. The placebo group received more heparin, both measured by total dose and by duration of infusion. Note that, despite the protocol recommendation to stop the heparin shortly after the procedure, subjects received heparin for a significant period of time (>10 hours in most cases) after end of procedure.

### 6.2.3.12.2c Concomitant Therapies used after Trial Initiation (cont)

Table 6.2.3.12.2.1 Administration of heparin in the RESTORE trial

	Tirofiban group (n=1071)	Placebo group (n=1070)	p value
<b>Total dose of heparin</b>			
0 Units	36 (3.4%)	30 (2.8%)	
1-4999 Units	19 (1.8%)	15 (1.4%)	
5000 to 9999 Units	200 (18.8%)	188 (17.8%)	
10000 to 19999 Units	760 (71.4%)	760 (71.8%)	
>20000 Units	49 (4.6%)	65 (6.1%)	
<b>Mean heparin dose</b>	<b>10,860.6</b>	<b>11,376.0</b>	<b>0.013</b>
<b>Duration of Heparin infusion</b>			
0 hrs	300 (28.0%)	284 (26.5%)	
>0 to <6	70 (6.5%)	63 (5.9%)	
6 to 12 hrs	145 (13.5%)	105 (9.9%)	
> 12 hrs	556 (51.9%)	618 (57.8%)	
<b>Mean duration of infusion (hrs)</b>	<b>18.8</b>	<b>20.3</b>	<b>0.035</b>

a. Data from NDA volume 1.55, tables 12 . Shown as n (%).

b. p values calculated using t test.

This difference in heparin dose did not lead to a large increase in the ACT, and was not a reflection of longer procedure time. The time that the procedure took, as well as the ACT during the procedure, were measured in a subset of the population. As shown below, the only difference was a slightly longer ACT in the tirofiban group. The difference is unlikely to be of clinical significance (10/270 secs, 3.7%).

Table 6.2.3.12.2.2 Details on initial procedures performed in the RESTORE trial<sup>a</sup>.

	Tirofiban (n=1071)	Placebo (n=1070)	p value
<b>Elapsed Time</b>			
Procedure (min)	52.4±35.8	54.9±43.9	0.381
Sheath removal (hrs)	12.7±8.7	13.2±10.1	0.857
Subject ambulation (hrs)	37.2±32.5	38.0±25.2	0.744
<b>ACT during procedure (secs)</b>	<b>273±92</b>	<b>263±83</b>	<b>0.081</b>

a. Data from NDA volume 1.55, tables 11. Shown as n (%).

b. p values calculated using chi square or t-test as appropriate.

Concomitant therapies were taken by all of the subjects in the trial. For most drugs, no significant difference existed between the three groups in terms of frequency of use (see NDA volume 1.55, ref 11, table 14 for full listing). The most common individual concomitant therapies were aspirin (used by approximately 98% of the total study population), nitroglycerin (87%), acetaminophen (38%) and metoprolol tartrate (57%).

A higher proportion of placebo subjects took dextran sulfate (2.0% vs. 0.7%, p=0.015), heparin (42.9% vs. 35.9%, p=0.001), quinapril (2.1% vs. 0.9%, p=0.023), verapamil (6.7% vs. 4.6%, p=0.032). A higher percentage of tirofiban subjects were taking ferrous sulfate (3.1% vs. 1.5%, p=0.020).

### 6.2.3.12.2d Primary Analyses of the RESTORE Trial Results

The primary endpoint in the RESTORE trial was the incidence of the following during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular shunt because of procedure failure. The results for the primary endpoint, including odds ratios (shown in bold) and p-values, are summarized in the table below. The proportions of patients with composite endpoint within 30 days was 10.3% (110/1071) in the tirofiban group and 12.2% (130/1070) in the placebo group. This difference between treatments represented an odds ratio of 0.828 (95% CI=[0.632, 1.084]), and a risk ratio of 0.834 (95% CI=[0.65, 1.08]), which represents a 17% risk reduction for an event for the tirofiban group. This difference was not significant (p=0.169). The difference between treatments in the individual components of the composite were all in the same direction, favoring tirofiban, except for death, which was rare and appeared to occur equally in the two groups.

6.2.3.12.2d Primary Analyses of the RESTORE Trial Results (cont)

Table 6.2.3.12.2d.1 Incidence of the combined endpoint and its components at 48 hours, 7, 30, and 180 days in the RESTORE trial. The primary endpoint is shaded.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	Odds Ratio (bold) & 95% CI	p value <sup>b</sup>
Combined endpoint at 48 hours <sup>d</sup>	58 (5.4%)	93 (8.7%)	<b>0.598</b> 0.425, 0.840	<b>0.003</b>
Combined endpoint at 7 days	81 (7.6%)	111 (10.4%)	<b>0.704</b> 0.522, 0.951	<b>0.022</b>
Combined endpoint at 30 days (primary endpoint)	110 (10.3%)	130 (12.2%)	<b>0.828</b> 0.632, 1.084	0.169
Combined endpoint at 180 days (secondary endpoint)	258 (24.1%)	290 (27.1%)	<b>0.853</b> 0.702, 1.037	0.110
CABG at 48 hours	10 (0.9%)	15 (1.4%)	<b>0.653</b> 0.291, 1.461	0.299
CABG at 7 days	13 (1.2%)	17 (1.6%)	<b>0.748</b> 0.402, 1.139	0.436
CABG at 30 days	20 (1.9%)	23 (2.2%)	<b>0.859</b> 0.469, 1.575	0.623
CABG at 180 days	59 (5.5%)	73 (6.8%)	<b>0.793</b> 0.556, 1.130	0.199
Repeat PTCA at 48 hours <sup>e</sup>	12 (1.1%)	34 (3.2%)	<b>0.343</b> 0.176, 0.666	<b>0.002</b>
Repeat PTCA at 7 days	29 (2.7%)	47 (4.4%)	<b>0.603</b> 0.377, 0.967	<b>0.036</b>
Repeat PTCA at 30 days	45 (4.2%)	58 (5.4%)	<b>0.766</b> 0.514, 1.142	0.191
Repeat PTCA at 180 days	168 (15.7%)	183 (17.1%)	<b>0.902</b> 0.717, 1.135	<b>0.378</b>
Stent placement at 48 hours <sup>f</sup>	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.096	<b>0.094</b>
Stent placement at 7 days	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.095	<b>0.094</b>
Stent placement at 30 days	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.096	<b>0.094</b>
Stent placement at 180 days	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.095	<b>0.094</b>
MI (fatal & non-fatal) at 48 hours	29 (2.7%)	47 (4.4%)	<b>0.599</b> 0.373, 0.960	<b>0.033</b>
MI (fatal & non-fatal) at 7 days	39 (3.6%)	57 (5.3%)	<b>0.665</b> 0.438, 1.010	<b>0.055</b>
MI (fatal & non-fatal) at 30 days	45 (4.2%)	61 (5.7%)	<b>0.720</b> 0.485, 1.069	<b>0.104</b>
MI (fatal & non-fatal) at 180 days	67 (6.3%)	81 (7.6%)	<b>0.809</b> 0.578, 1.132	<b>0.216</b>
Death at 48 hours	2 (0.2%)	2 (0.2%)	<b>0.974</b> 0.136, 6.953	<b>0.979</b>
Death at 7 days	4 (0.4%)	4 (0.4%)	<b>0.988</b> 0.246, 3.964	<b>0.986</b>
Death at 30 days	9 (0.8%)	8 (0.7%)	<b>1.126</b> 0.433, 2.930	<b>0.808</b>
Death at 180 days	19 (1.8%)	15 (1.4%)	<b>1.274</b> 0.644, 2.521	<b>0.487</b>

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used.

b. p value per the sponsor based on logistic regression analysis, and confirmed by FDA analysis (Dr. James Hung).

c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated.

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a stent because of procedural failure.

e. Stent placement refers to those stents placed after the initial PTCA for procedure failure.

f. Includes both PTCA and atherectomy.

### 6.2.3.12.2d Primary Analyses of the RESTORE Trial Results (cont)

The sponsor also analyzed the time-course of the effect of tirofiban on the composite endpoint, and the results are shown below, first for O-30 days, and then for O-180 days. The Kaplan-Meier curves show the proportion of subjects experiencing the composite endpoint through 30 and 180 days, analyzed for the intent-to-treat population.

Figure 6.2.3.12.2d.1 Incidence of the combined endpoint for days O-30 in the RESTORE trial.

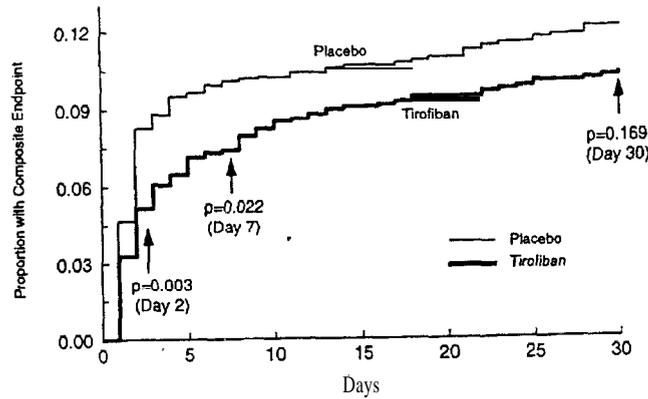
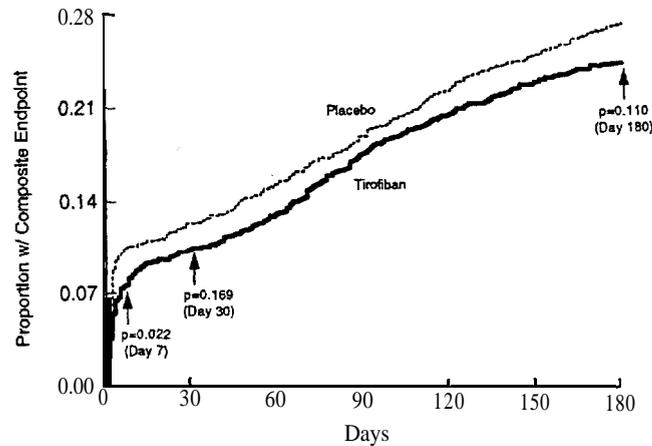


Figure 6.2.3.12.2d.2 Incidence of the combined endpoint for days O-180 in the RESTORE trial.



The FDA also performed an analysis of the same data, using Pearson's chi square, and the results are shown below.

Table 6.2.3.12.2d.2 Incidence of the combined endpoint and its components at 48 hours, 7, 30, and 180 days in the RESTORE trial, analyzed using chi square<sup>a</sup>. The primary endpoint is shaded.

Clinical endpoint	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	p value by chi square <sup>b</sup>
Combined endpoint at 48 hours <sup>d</sup>	58 (5.4%)	93 (8.7%)	0.003
Combined endpoint at 7 days	81 (7.6%)	111 (10.4%)	0.023
Combined endpoint at 30 days (primary endpoint)	110 (10.3%)	130 (12.2%)	0.168
Combined endpoint at 180 days (secondary endpoint)	258 (24.1%)	290 (27.1%)	0.110

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used.

b. p value per the FDA using Pearson's chi square.

c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated.

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure.

### 6.2.3.12.3 Subgroup & Post-hoc Analyses of the RESTORE Trial Results

#### Subgroup analyses of the RESTORE trial results

The sponsor performed a series of subgroup analyses, and the results are shown below. Based on a sponsor-performed regression analysis, certain factors determined whether a subject experienced the combined endpoint are shaded. Of note, four characteristics were associated with a significantly improved outcome, as judged by the combined primary endpoint (shown as shaded in the table):

- 1) a successful outcome of the procedure;
- 2) having a single lesion rather than multiple lesions;
- 3) not having received a stent; and
- 4) not receiving any heparin (compared with receipt of heparin for >6 hrs post-angioplasty).

Subjects in the tirofiban group were significantly more likely to have a successful procedure (92.1% vs 89.5), while subjects in the placebo group were significantly more likely to have only one lesion (79.4% vs. 76.6%) (see table 6.2.3.12.2.1 above). Subjects in the placebo group also received more heparin, for a longer period of time, than did the tirofiban group (see table 6.2.3.12.2.1 above).

Table 6.2.3.12.3.1 Incidence of the combined endpoint and its components at 30 days in RESTORE trial<sup>a</sup>.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070
<b>Age</b>		
<65	67/699 (9.6%)	84/707 (11.9%)
65 to 74	31/287 (10.8%)	35/286 (12.2%)
≥75	12/85 (14.1%)	11/77 (14.3%)
<b>Gender</b>		
Female	34/294 (11.6%)	39/288 (13.5%)
Male	76/777 (9.8%)	91/782 (11.6%)
<b>Race</b>		
Caucasian	95/943 (10.1%)	118/962 (12.3%)
Other	15/128 (11.7%)	12/108 (11.1%)
<b>Weight</b>		
Light (<mean)	64/594 (11.8%)	67/543 (12.3%)
Heavy (≥mean)	46/477 (9.6%)	63/527 (12.0%)
<b>Inclusion Criterion</b>		
Unstable angina	78/725 (10.8%)	90/728 (12.4%)
Acute MI	32/346 (9.3%)	40/342 (11.7%)
Primary PTCA	7/71 (9.9%)	8/63 (12.7%)
Nonprimary	25/274 (9.1%)	32/279 (11.5%)
<b>Procedure</b>		
PTCA	103/985 (10.5%)	119/997 (11.9%)
Atherectomy	7/86 (10.8%)	11/73 (15.1%)
<b>Center</b>		
≥50 subjects	26/290 (8.1%)	30/296 (10.1%)
All others	84/781 (10.8%)	100/774 (12.9%)
<b>Aspirin Pre-procedure</b>		
Yes	107/1041 (10.2%)	125/1048 (11.9%)
No	3/30 (10%)	5/22 (22.7%)
<b>Initial Procedure</b>		
Successful	75/986 (7.7%)	76/958 (8.6%)
Unsuccessful	34/84 (40.5%)	48/112 (42.9%)
Stent placed	28/80 (35%)	41/95 (43.2%)
Stent placed (excluding endpoints)	17/80 (21.3%)	23/95 (24.2%)
No stent placed	82/990 (8.3%)	89/975 (9.1%)
<b>Lesions dilated initially</b>		
Single	75/819 (9.2%)	92/844 (10.9%)
Multiple	34/249 (13.7%)	37/219 (16.9%)
<b>Vessels dilated initially</b>		
Single	96/974 (9.9%)	116/973 (12.0%)
<b>Heparin Post-procedure</b>		
≥6 hours	76/701 (10.9%)	102/723 (14.1%)
<6 hours	26/300 (8.7%)	20/284 (7.0%)

a. Data from NDA 20-912, volume 1.55, ref I I, tables 24. Intent-to-treat population is used. NA= not applicable

b. 95% confidence intervals (CI) per the sponsor based on logistic regression analysis. Shaded variables had a significant effect on the outcome (% of subjects with clinical endpoint).

### 6.2.3.12.3 Subgroup & Post-hoc Analyses of the RESTORE Trial Results (cont)

#### Angiographic substudy from the RESTORE trial results

The sponsor collected 211 subjects in the tirofiban arm and 205 subjects in the placebo arm who had baseline and follow-up coronary angiography. The treatment groups were similar in their vessel reference diameter (2.78mm in tirofiban, 2.70mm in placebo), and in the initial minimal lumen diameter (0.57mm for the tirofiban group, 0.53mm in placebo). The final lumen diameter post-PTCA was also similar (1.89mm in both groups). The table below shows the results from the three ways used by the sponsor to measure efficacy of tirofiban to slow restenosis. No significant differences in the incidence rates were detected.

Table 6.2.3.12.3.2 Repeat angiogram results from the RESTORE trial<sup>a</sup>.

	Tirofiban (n=1071)	Placebo (n=1070)	p value
Loss of ≥50% of lumen diameter gain after initial PTCA	105/211 (40%)	103/205 (50%)	0.99
<50% stenosis at follow-up <sup>c</sup>	100/196 (51%)	110/193 (57%)	0.26
Loss of lumen diameter ≥0.72mm	88/211 (42%)	90/205 (44%)	0.69

a. Data from NDA volume 1.55, page 10831. Shown as n (%).

b. p values calculated using chi square.

c. Subset of subjects with <50% stenosis after initial PTCA.

#### Cardiac procedures

The treatment groups were also compared with regards to the number of cardiac procedures at any time in the first 30 days of the trial, other than those procedures required by protocol or procedures that constituted an endpoint. No evidence of a difference between the two groups was detected.

Table 6.2.3.12.3.3 Cardiac procedures performed after initial PTCA/atherectomy in the RESTORE trial<sup>a</sup>.

	Tirofiban (n=1071)	Placebo (n=1070)	p value
Any cardiac procedures	435 (40.6%)	442 (41.3%)	0.745
ECHO without Doppler	44 (4.1%)	48 (4.5)	0.672
ECHO with Doppler	87 (8.1%)	93 (8.7%)	0.641
ETT without imaging	66 (6.2%)	72 (6.7%)	0.599
ETT with nuclear perfusion imaging	11 (1.0%)	18 (1.7%)	0.197
Radionuclide ventricular imaging	8 (0.7%)	2 (0.2%)	0.109
Right heart catheterization	16 (1.5%)	14 (1.3%)	0.855
IABP	18 (1.7%)	26 (2.4%)	0.228
Stress-ECHO	1 (0.1%)	2 (0.2%)	0.625
Stress-nuclear imaging	17 (1.6%)	11 (1.0%)	0.342
Rest nuclear perfusion imaging	7 (0.7%)	8 (0.7%)	0.803
Other cardiac procedure	291 (27.2%)	269 (25.1%)	0.302

a. Data from NDA volume 1.55, ref. 11, table 25 and electronic datasets. Shown as n (%).

b. p value calculated using chi square analysis.

#### Reanalysis of RESTORE trial combined endpoint using ‘urgent/emergent revascularization’

The primary endpoint in the RESTORE trial, as stated above, was the occurrence of the following composite endpoint during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure. After the study results were known, the sponsor raised the issue of comparability of this endpoint and endpoints used in other trials of platelet inhibitors. Specifically, they contrasted their primary endpoint, which includes ‘CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia,’ with the endpoints used in other trials of IIb/IIIa receptor antagonists, suggesting that the other trials included as endpoints only those subjects with whose PTCA or CABG was ‘emergent.’

Per the sponsor, recurrent ischemia was generally evidenced by a recurrent clinical ischemic event (e.g., angina, MI) or provocative testing (e.g., stress testing) and was denoted by the investigators on the CRF. This form, in addition to other supportive documents (such as lab sheets for CPK-MB) were provided to the Endpoint Adjudication Committee members for adjudication of endpoints. This issue is discussed further in section 7.0.

After the initial analysis was performed, the sponsor performed a post-hoc analysis in which the composite endpoint was redefined to include CABG or revascularizations (for original target or non-target vessel) for urgent or emergent indications only.

### 6.2.3.12.3 Subgroup & Post-hoc Analyses of the RESTORE Trial Results (cont)

For the blinded re-adjudication or revascularization endpoints in this post-hoc analysis, a letter was sent outlining new criteria for determining whether or not the procedure was done on an urgent/emergent basis. In general, this was defined as a procedure that required a 'rush' to the cath laboratory for a procedure that could not have been performed on an elective basis (e.g., not wait 24 hours). No criteria for 'emergent' events was predefined in the protocol, and the CRFs used to record subject outcomes do not have a check box for any emergent outcome.

The results of this post-hoc analysis, including only emergency angioplasty or bypass surgery as components of the endpoints, adjudicated by the Endpoint Committee, are shown in the table below. This analysis was based on 67/103 of the PTCAs (65%) and 27/43 (63%) of the CABGs that were determined to be urgent/emergent by the above criteria. The 30-day event rates for the combined endpoint using only 'emergency CABG/ PTCA were 10.5% for the placebo group and 8.0% for the tirofiban group ( $p=0.052$ , 95% CI=0.57 to 1.00). In addition, the emergency PTCA component was significant, with a rate of 4.0% in the placebo group and 2.3% in the tirofiban group ( $p=0.027$ ). There was no difference in the rates of emergency CABG between the tirofiban and placebo groups.

Results at Days 2 and 7 were similar to those using the protocol definition of the composite (including 'non-urgent/emergent revascularization). The sponsor suggested that this is because PTCAs and CABGs that occurred early were more likely to be emergency or urgent procedures.

Table 6.2.3.12.3.4 'Primary endpoint' including only urgent/emergent revascularization procedures from the RESTORE trial".

	Tirofiban n=1071	Placebo n=1070	Odds Ratio (bold) & 95% CI	p value <sup>b</sup>
Combined endpoint at 48 hours	56 (5.2%)	93 (8.7%)	0.576	0.002
Combined endpoint at 7 days	74 (6.9%)	105 (9.8%)	0.490, 0.813	0.015
Combined endpoint at 30 days	86 (8.0%)	112 (10.5%)	0.680 0.499, 0.928	0.052
Emergency CABG at 48 hours	<b>10 (0.9%)</b>	14 (1.3%)	0.746 0.556, 1.003	0.422
Emergency CABG at 7 days	<b>12 (1.1%)</b>	15 (1.4%)	0.705 0.311, 1.595	0.539
Emergency CABG at 30 days	12 (1.1%)	15 (1.4%)	0.787 <b>0.366, 1.690</b>	0.539
Emergency repeat PTCA at 48 hours	10 (0.9%)	35 (3.3%)	0.276 0.136, 0.561	<0.001
Emergency repeat PTCA at 7 days	22 (2.1%)	42 (3.9%)	<b>0.511</b>	0.012
Emergency repeat PTCA at 30 days	25 (2.3%)	43 (4.0%)	0.303, 0.863 0.569 0.345, 0.938	0.027
Stent placement at 48 hours	16 (1.5%)	27 (2.5%)	0.586 0.314, 1.096	0.094
Stent placement at 7 days	16 (1.5%)	27 (2.5%)	0.586	0.094
Stent placement at 30 days	<b>16 (1.5%)</b>	27 (2.5%)	0.314, 1.095 0.586 0.314, 1.096	0.094
MI (both fatal and non-fatal) at 48 hours	<b>29 (2.7%)</b>	47 (4.4%)	0.599 0.373, 0.960	0.033
MI (both fatal and non-fatal) at 7 days	39 (3.6%)	57 (5.3%)	0.665 0.438, 1.010	0.055
MI (both fatal and non-fatal) at 30 days	45 (4.2%)	61 (5.7%)	0.720 0.485, 1.069	0.104
Death at 48 hours	2 (0.2%)	2 (0.2%)	0.974	0.979
Death at 7 days	4 (0.4%)	4 (0.4%)	0.136, 6.953 0.988	0.986
Death at 30 days	<b>9 (0.8%)</b>	8 (0.7%)	0.246, 3.964 1.126 0.433, 2.930	0.808

a. Data from NDA #20-912 Aggrastat, ref 11, table 22 and electronic datasets 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.

b. post-hoc p value calculated using chi square, and confirmed by FDA analysis. No adjustment made for post-hoc analysis or multiplicity.

### 6.2.3.13 Safety Outcomes

The adverse **events**, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The first table summarizes the adverse clinical events that occurred in the RESTORE trial. The number of subjects with AEs and SAEs was higher in the tirofiban group, as was the number of subjects with drug-related AEs, serious- and drug-related AEs, and discontinuations due to and AE.

Table 6.2.3.13.1 Clinical adverse experience (AE) summary from the RESTORE trial<sup>a</sup>.

Clinical event	Tirofiban n=1071	Placebo n=1070
<b>With any AE</b>	942 (88.0%)	887 (82.9%)
<b>Without any AE</b>	129 (12.0%)	183 (17.1%)
<b>With Serious AE (SAE)</b>	200 (18.7%)	176 (16.4%)
<b>With drug-related AE<sup>b</sup></b>	474 (44.3%)	340 (31.8%)
<b>With serious and drug-related AEs</b>	27 (2.5%)	16 (1.5%)
<b>Discontinued due to an AE<sup>c</sup></b>	109 (10.2%)	91 (8.5%)
<b>Discontinued due to Lab AE</b>	9 (0.8%)	2 (0.2%)
<b>Deaths</b>	9 (0.8%)	8 (0.7%)

a. Data from NDA volume 1.47, ref. 7, table 25, and electronic datasets.

b. Felt to be possibly, probably, or definitely drug-related by individual investigators.

c. Four subjects had both lab and clinical AEs leading to discontinuation, and are counted in both categories for purposes of adverse experiences. Three of these are counted in the discontinuation table as AE-bleeding and one is counted as a laboratory AE.

#### 6.2.3.13.1 Comparisons of Defined Safety Endpoints

The deaths, serious adverse *events*, and adverse events by body system will be considered in section 8.1 and 8.2 below. The section below will comment on the following specific safety parameters from the RESTORE trial: deaths; subject discontinuations; bleeding AEs; and thrombocytopenia.

#### 6.2.3.13.2 Comments on Specific Safety Parameters

##### Deaths

There were 9 deaths in the tirofiban group (0.8%), and 8 in the placebo group (0.7%) through 30 days. Narratives of the individual subject deaths can be found in section 14.0.3 (appendix 2). A discussion of the causes of death in the entire safety database can be found in section 8.1.1<sup>1</sup>. The rates of death at each of the time points are summarized below.

Table 6.2.3.13.2.1 Deaths in the RESTORE trial<sup>a</sup>

Time of Follow-up	Tirofiban n=1071	Placebo n=1070	Total n=2141
<b>48 hours</b>	2 (0.2%)	2 (0.2%)	4 (0.2%)
<b>7 days</b>	4 (0.4%)	4 (0.4%)	8 (0.4%)
<b>30 days</b>	9 (0.8%)	8 (0.7%)	17 (0.8%)
<b>180 days</b>	19 (1.8%)	15 (1.4%)	34 (1.6%)

a. Data from NDA volume 1.55, reference 11, table 22.

##### Subject discontinuations

The first table shows the incidence of clinical AEs leading to subject discontinuation. Significantly more subjects in the tirofiban group were discontinued for bleeding AEs. A list of all subject discontinuations for the RESTORE trial appears in section 16.0 (appendix 4).

Table 6.2.3.13.2.2 Reasons for subject discontinuation in the RESTORE trial<sup>a</sup>.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	p value <sup>b</sup>
<b>Bleeding AE</b>	41 (3.8%)	13 (1.2%)	<0.001
<b>Non-bleeding AE</b>	24 (2.2%)	21 (2.0%)	0.655
<b>Stent usage</b>	60 (5.6%)	76 (7.1%)	0.152

a. Data from NDA vol. 1.55, ref 11, table 30 and electronic datasets.

b. p value calculated using chi square test.

c. Both groups received heparin unless otherwise contraindicated

### 6.2.3.13.2 Comments on Specific Safety Parameters (cont)

The clinical AEs and laboratory AEs that resulted in discontinuation in the RESTORE trial are summarized in the two tables below, for all AEs occurring  $\geq 0.5\%$  of either treatment group. Note the significant increase in post-operative bleeding in the tirofiban group relative to placebo. The increased number of discontinuations in the Digestive System for tirofiban comes from GI bleeding, discussed in section 8.1 and 8.2. The bleeding discontinuations will be discussed below. Laboratory AEs related to bleeding were more common in the tirofiban group.

Table 6.2.3.13.2.3 Clinical AEs leading to discontinuation in the RESTORE trial<sup>a</sup>.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	p value <sup>b</sup>
Any Adverse Experience	109 (10.2%)	91 (8.5%)	0.160
Body as a Whole/Site Unspecified)	5 (0.5%)	4 (0.4%)	1.000
<b>Cardiovascular System</b>	85 (7.9%)	77 (7.2%)	0.567
Bleeding, postoperative	22 (2.0%)	6 (0.5%)	0.004
Dissection, coronary artery	42 (3.9%)	52 (4.9%)	0.294
Hematoma <sup>c</sup>	10 (0.9%)	3 (0.3%)	0.091
Occlusion, coronary artery	1 (0.1%)	7 (0.7%)	0.039
<b>Digestive System</b>	14 (1.3%)	2 (0.2%)	0.004
<b>Metabolic, Nutritional, Immune</b>	0 (0.0%)	1 (0.1%)	0.500
<b>Nervous System/Psychiatric</b>	4 (0.4%)	4 (0.4%)	1.000
<b>Respiratory System</b>	4 (0.4%)	2 (0.2%)	0.687
<b>Skin/Skin Appendage</b>	4 (0.4%)	3 (0.3%)	1.000
<b>Special Sense</b>	7 (0.7%)	1 (0.1%)	1.000
<b>Urogenital System</b>	7 (0.7%)	1 (0.1%)	0.070

a. Data from NDA vol. 1.55, ref 11, table 31 and electronic datasets.

b. p value calculated using chi square test

c. Both groups received heparin unless otherwise contraindicated.

Table 6.2.3.13.2.4 Laboratory AEs, including AEs leading to discontinuation, in RESTORE<sup>a</sup>.

	Tirofiban <sup>b</sup> n=1071	Placebo <sup>b</sup> n=1070
With any laboratory AE	272 (25.4%)	256 (23.9%)
Without any laboratory AE	799 (74.6%)	814 (76.1%)
With drug-related laboratory AE	146 (13.6%)	137 (12.8%)
With any serious laboratory AE	4 (0.4%)	4 (0.4%)
With serious drug-related laboratory AE	4 (0.4%)	2 (0.2%)
Discontinued due to a laboratory AE	9 (0.8%)	2 (0.2%)
Bleeding lab AE	8 (0.7%)	2 (0.2%)

a. Data from NDA vol. 1.55, ref 11, table 32 and electronic datasets.

b. Both groups received heparin unless otherwise contraindicated.

6.2.3.13.2 Comments on Specific Safety Parameters (cont)

Bleeding AEs in the RESTORE trial

The sponsor summarized the bleeding AEs that occurred in the RESTORE trial. They reported that significantly more subjects in the tirofiban group had at least one episode of bleeding, as shown in the table below.

Table 6.2.3.13.2.5 Bleeding AEs in the RESTORE trial<sup>a</sup>.

	Tirofiban <sup>a</sup> n=1071	Placebo <sup>c</sup> n=1070	p value <sup>b</sup>
<b>An bleeding complication</b>	<b>590 (55.1%)</b>	<b>434 (40.6%)</b>	<b>&lt;0.001</b>
<b>No bleeding complication</b>	<b>481 (44.9%)</b>	<b>636 (59.4%)</b>	

a. Data from NDA vol. 1.55, ref 11, table 35. Subjects with more than one AE were counted only once.

b. p value calculated using chi square test.

c. Both groups received heparin unless otherwise contraindicated.

More subjects in the tirofiban group also had at least one episode of major bleeding, either by protocol definition or as judged by the TIMI classification.

Table 6.2.3.13.2.6 Major bleeding AEs in the RESTORE trial<sup>a</sup>.

	Tirofiban <sup>a</sup> n=1071	Placebo <sup>c</sup> n=1070	p value <sup>b</sup>
<b>Major Bleeding:</b>	<b>57 (5.3%)</b>	<b>40 (2.7%)</b>	<b>0.096</b>
Hemoglobin drop >5 g/dl	<b>25 (2.3%)</b>	19 (1.8%)	
Transfusion of 2 units or more	<b>38 (3.5%)</b>	<b>24 (2.2%)</b>	
Corrective surgery	<b>3 (0.3%)</b>	<b>2 (0.2%)</b>	
Intracranial hemorrhage	1 (0.1%)	<b>3 (0.3%)</b>	
Retroperitoneal hemorrhage	<b>6 (0.6%)</b>	<b>3 (0.3%)</b>	
<b>TIMI Bleeding: any</b>	<b>156 (14.6%)</b>	<b>90 (8.4%)</b>	<b>&lt;0.001</b>
Major	<b>24 (2.2%)</b>	<b>17 (1.6%)</b>	
Minor	<b>129 (12.0%)</b>	<b>67 (6.3%)</b>	
Loss/ No site identified	<b>3 (0.3%)</b>	<b>6 (0.6%)</b>	

a. Data from NDA vol. 1.55, ref 11, table 36.

b. p value calculated using chi square test.

c. Both groups received heparin unless otherwise contraindicated.

6.2.3.13.2 Comments on Specific Safety Parameters (cont)

**Bleeding AEs in the RESTORE trial (cont)**

The sites for bleeding are summarized in the table below. For details of all bleeding AEs related to tirofiban see integrated safety review, section 8.1. Overall, tirofiban subject had significantly more bleeding at any site ( $p < 0.001$ ), at catheterization sites ( $p < 0.001$ ), hematomas ( $p < 0.001$ ), oral ( $p < 0.001$ ), nasal ( $p < 0.001$ ), GU/hematuria ( $p < 0.001$ ), and GI ( $p = 0.047$ ).

Table 6.2.3.13.2.7 Major bleeding AE: arranged by site of bleeding the RESTORE trial.

Bleeding Site	Tirofiban <sup>d</sup> n=1071	Placebo <sup>d</sup> n=1070	p-value
<b>Any site</b>			
Oozing	240 (22.4%)	172 (6.1%)	<0.001
Mild	199 (18.6%)	171 (16.0%)	
Moderate	123 (18.6%)	74 (6.9%)	
Severe	21 (2.0%)	11 (1.0%)	
Life-threatening	7 (0.7%)	6 (0.6%)	
<b>IV site</b>			
Oozing	5 (0.5%)	3 (0.3%)	0.156
Mild	6 (0.6%)	3 (0.3%)	
Moderate	1 (0.1%)	1 (0.1%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>Catheter site</b>			
Oozing	335 (31.3%)	226 (21.1%)	<0.001
Mild	45 (4.2%)	46 (4.3%)	
Moderate	37 (3.5%)	17 (1.6%)	
Severe	2 (0.2%)	2 (0.2%)	
Life-threatening	1 (0.1%)	0 (0%)	
<b>Hematoma</b>			
Oozing	5 (0.5%)	2 (0.2%)	<0.001
Mild	95 (8.9%)	71 (6.6%)	
Moderate	69 (6.4%)	35 (3.3%)	
Severe	6 (0.6%)	3 (0.3%)	
Life-threatening	0 (0%)	1 (0%)	
<b>Oral</b>			
Oozing	13 (1.2%)	2 (0.2%)	<0.001
Mild	22 (2.1%)	5 (0.5%)	
Moderate	1 (0.1%)	2 (0.2%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>Nasal</b>			
Oozing	16 (1.5%)	1 (0.1%)	<0.001
Mild	26 (2.4%)	4 (0.4%)	
Moderate	4 (0.4%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>GU/ Hematuria</b>			
Oozing	9 (0.8%)	9 (0.8%)	0.022
Mild	77 (7.2%)	52 (4.9%)	
Moderate	25 (2.3%)	18 (1.7%)	
Severe	0 (0%)	3 (0.3%)	
Life-threatening	0 (0%)	0 (0%)	
<b>GI</b>			
Oozing	1 (0.1%)	2 (0.2%)	0.047
Mild	16 (1.5%)	12 (1.1%)	
Moderate	9 (0.8%)	3 (0.3%)	
Severe	5 (0.5%)	1 (0.1%)	
Life-threatening	2 (0.2%)	1 (0.1%)	

6.2.3.13.2 Comments on Specific Safety Parameters (cont)  
Bleeding AEs in the RESTORE trial (cont)

Table 2.3.13.2.7 Major bleeding AEs by site in the RESTORE trial (cont).

Bleeding Site	Tirofiban n=1071	Placebo n=1070	p-value
<b>Hemoptysis</b>			
Oozing	0 (0%)	0 (0%)	0.404
Mild	7 (0.7%)	5 (0.5%)	
Moderate	1 (0.1%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	
<b>Intracranial</b>			
Oozing	0 (0%)	0 (0%)	0.317
Mild	0 (0%)	0 (0%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Life-threatening	1 (0.1%)	2 (0.2%)	
<b>Retroperitoneal</b>			
Oozing	0 (0%)	0 (0%)	0.319
Mild	1 (0.1%)	0 (0%)	
Moderate			
Severe	3 (0.3%)	1 (0.1%)	
Life-threatening	1 (0.1%)	2 (0.2%)	
<b>Other<sup>c</sup></b>			
Oozing	6 (0.6%)	0 (0%)	0.072
Mild	5 (0.5%)	5 (0.5%)	
Moderate	0 (0%)	2 (0.2%)	
Severe	1 (0.1%)	1 (0.1%)	
Life-threatening	3 (0.3%)	0 (0.3%)	
<b>Unknown</b>			
Oozing	0 (0%)	2 (0.2%)	0.138
Mild	4 (0.4%)	11 (1.0%)	
Moderate	5 (0.5%)	8 (0.7%)	
Severe	4 (0.4%)	2 (0.2%)	
Life-threatening	0 (0%)	0 (0%)	

a. Data from NDA vol. 1.55, ref 11, table 36. Definitions of categories can be found in section 8.1.7.3

b. p value calculated using chi square test.

c. Other category includes three subjects with pericardial bleeding, considered to be life-threatening

d. Both groups received heparin unless otherwise contraindicated.

6.2.3.13.2 Comments on Specific Safety Parameters (cont)  
Bleeding AEs in the RESTORE trial (cont)

Transfusion in the RESTORE trial

The results of the transfusion analyses for the RESTORE trial are summarized in the table below. The proportions of subjects requiring any transfusion and those requiring a transfusion of packed RBCs were higher in the tirofiban group than in the placebo group,  $p=0.031$  and  $p=0.049$ , respectively. There was no difference between treatments in the number of units of PRBCs transfused, but more subjects in the tirofiban +heparin group received transfusion of PRBCs than in the placebo +heparin group: 43 (4.0%) vs. 22 (2.4%)  $p=0.049$ .

Table 6.2.3.13.2.8 Percent of subjects requiring transfusions in the RESTORE trial<sup>a</sup>.

Type of transfusion	Tirofiban (N=1071)	Placebo (N=1070)	P-value
<b>Any Transfusion</b>			0.031
No	1025 (95.7%)	1043 (97.5%)	
Yes	46 (4.3%)	27 (2.5%)	
<b>Whole Blood</b>			1.000
No	1069 (99.8%)	1069 (99.9%)	
Yes	2 (0.2%)	1 (0.1%)	
<b>FFP</b>			1.000
No	1069 (99.8%)	1068 (99.8%)	
Yes	2 (0.2%)	2 (0.2%)	
<b>PRBC</b>			0.049
No	1028 (96.0%)	1044 (97.6%)	
Yes	43 (4.0%)	26 (2.4%)	
<b>Cryoprecipitates</b>			0.500
No	1071 (100.0%)	1069 (99.9%)	
Yes	0 (0.0%)	1 (0.1%)	
<b>Platelets</b>			0.625
No	1070 (99.9%)	1068 (99.8%)	
Yes	1 (0.1%)	2 (0.2%)	
<b>Other</b>			0.500
No	1069 (99.8%)	1070 (100.0%)	
Yes	2 (0.2%)	0 (0.0%)	

a. Data from sponsor at request of medical reviewer.

Table 6.2.3.13.2.9 Number of PRBC units transfused per subject in the RESTORE trial<sup>a</sup>.

PRBCs transfused	Tirofiban (N=1071) n (%)	Placebo (N=1070) n (%)	p-value
0	1028 (96.0)	1044 (97.6)	0.854
1	7 (0.7)	3 (0.3)	
2	20 (1.9)	13 (1.2)	
3	3 (0.3)	2 (0.2)	
4	5 (0.5)	5 (0.5)	
5 or more units	8 (0.7)	3 (0.3)	
Mean	2.95 (---)	3.88 (---)	

a. Data from sponsor at request of medical reviewer.

Thrombocytopenia

Twelve of 1071 subjects in the tirofiban group (1.1%) and 9/1070 in the placebo group (0.8%,  $p=0.66$ ) experienced a drop in platelet count to  $<90,000/\text{mm}^3$ . Of these subjects, two of the tirofiban and one of the placebo subjects experienced thrombocytopenia following a CABG, and two placebo subjects had it following intra-aortic balloon placement. Two of the subjects died in the placebo group (AN 1425 and AN 1445): in neither case was the thrombocytopenia causative (see death summaries).

Table 6.2.3.13.2.10 Incidence of decreased platelet counts in PRISM<sup>a</sup>.

Lab adverse event	Tirofiban (N=1071)	Placebo (N=1070)
Platelet count decrease to $<100,000/\text{mm}^3$	16 (1.6%)	16 (1.6%)
Platelet count decrease to $<90,000/\text{mm}^3$	12 (1.1%)	9 (0.8%)
Platelet count decrease to $<50,000/\text{mm}^3$	2 (0.2%)	2 (0.2%)
Platelet count decrease to $<20,000/\text{mm}^3$	NA	NA

a. Data from NDA volume 1.55, ref. 11, appendix 4.1.2.

#### 6.2.3.14 RESTORE Efficacy Summary

The two groups of subjects in the RESTORE trial were fairly balanced as regards demographics and clinical presentation at time of entry into the trial (see tables 6.2.3.12.1.1 to 6.2.3.12.1.3, p. 142). The subjects in the placebo arm were more likely to have valvular heart disease (4.1% vs. 2.6%,  $p=0.056$ ), and to have had prior coronary angiography (34.4% vs. 30.1%,  $p=0.037$ ). Subjects in the tirofiban group were significantly more likely to have a successful PTCA/ atherectomy (92.1% vs 89.5%), while subjects in the placebo group were significantly more likely to have only one lesion (79.4% vs. 76.6%) (see table 6.2.3.12.2.1 above, p. 145).

The two study groups were also well-balanced with regard to duration of tirofiban infusion (see table 6.2.3.12.2.3, p. 145). However, subjects in the placebo group received significantly more heparin (see table 6.2.3.12.2.1, p. 146).

With few exceptions, the groups were also well-balanced with regard to concomitant medications used during the trial. However, a higher percentage of the placebo subjects were receiving heparin at time of entry into the trial (42.9% vs. 35.9%,  $p=0.001$ ).

1. The RESTORE trial failed to demonstrate a significant reduction in the incidence of the pre-specified primary endpoint in the tirofiban group, when compared with the placebo group. The primary endpoint for the RESTORE trial was the occurrence of the following composite endpoint during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure. The sponsor's calculated p value for this endpoint was 0.169, comparing the tirofiban group with placebo. There was, however, a trend favoring tirofiban at this time point (see table 6.2.3.12.2d.1, p. 147). At 48 hours and 7 days, there was a nominally significant association between tirofiban administration and a reduction in the incidence of the composite endpoint.

2. Analysis of the components of the primary endpoint found nominally significantly fewer PTCAs and MIs (fatal and non-fatal) in the tirofiban arm at early time points (48 hrs and 7 days), but no difference in the incidence of CABG or death (p. 147).

3. The sponsor performed a post-hoc analysis of the data, suggesting that their inclusion of some subjects who received non-emergent CABG or PTCA 'diluted' the beneficial effect of tirofiban. This reanalysis suggested a significant benefit of tirofiban on the occurrence of a 'revised' primary endpoint, including only those subjects who underwent emergent PTCA/ CABG. Further discussion of this analysis is to be found in the integrated efficacy summary in section 7.0 (section 7.0.2.1b, p. 159).

#### 6.2.3.15 RESTORE Safety Summary

The safety profile of tirofiban will be examined in greater detail in the integrated safety summary (sections 8.1-8.3). The following comments relate to the data presented above.

1. Death occurred at a similar, low rate in both tirofiban and placebo groups (table 6.2.3.13.2.1, p. 152). While several of the deaths were associated with bleeding, none could be clearly related to tirofiban administration.

2. Clinical AEs, including bleeding AEs, occurred more frequently in the tirofiban (+heparin) arm. More subjects were also withdrawn from the tirofiban (+heparin) arm due to clinical AEs, including AEs related to bleeding (see table 6.2.3.13.2.2, p. 152). These bleeding AEs occurred in the cardiovascular system, related to procedures, as well as the GI and GU systems (see table 6.2.3.13.2.3, p. 153).

3. Bleeding AEs, as discussed above, were more frequent in the tirofiban arm (see table 6.2.3.13.2.5, p. 154). While the majority of these bleeding events were minor in nature, there were more retroperitoneal bleeds, more need for transfusions, and more 'Major' bleeds judged by the TIMI scale in the tirofiban group (see table 6.2.3.13.2.6, p. 154).

4. Thrombocytopenia was not significantly more common in the tirofiban (+heparin) group than in the placebo (+heparin) group (1.1% vs. 0.8%,  $p=0.66$ , see table 6.2.3.13.2.10, p. 157).

5. More subjects in the tirofiban (+heparin) group received transfusion of packed RBCs than in the placebo (+heparin) group: 43 (4.0%) vs. 22 (2.4%),  $p=0.049$ , see table 6.2.3.13.2.8 and 6.2.3.13.2.9, p. 157).

6. No unexpected toxicities of tirofiban were identified from the database by this reviewer.

## 7.0 Integrated Review of Efficacy

In the integrated review of efficacy, the efficacy database, which consists of the six trials reviewed above, will be summarized, along with secondary materials, as an aid towards the determination of clinical efficacy for tirofiban.

First, the data on the physiological effects of tirofiban will be summarized. The pharmacokinetics come from the phase II studies (#005, #007 and #008), as well as the pharmacokinetic subgroup of the PRISM trial. The data on the effect of tirofiban on clot formation and restenosis will also be summarized.

Next, the success of the three pivotal trials at meeting their pre-specified primary and secondary endpoints will be reviewed. As part of these analyses, the results of each trial will be compared with trials using other GP IIb/IIIa platelet receptor-blockers on similar subject populations (i.e., post-PTCA or UAP/NQWMI irrespective of procedures). An integrated review of these trials can also be found in appendix seven, section 19.0 (Efficacy Summary for Reopro, Integrilin, and Plavix).

Following this, the sub-group and post-hoc analyses performed by the sponsor and by the FDA will be reviewed. These analyses will be broken into two groups, according to the population studied: the post-PTCA sub-group of the UAP/NQWMI population (RESTORE trial); and the larger UAP/NQWMI group (irrespective of procedure) (PRISM-PLUS and PRISM trials).

Due to time-constraints, no assessment of the success of the overall database at establishing a clinical benefit for tirofiban is included. Please see the review by Shaw Chen, M.D. for further discussion in this regard.

### 7.0.1 Physiological Effect of Tirofiban

The physiological effect of tirofiban to block the activation of platelets with ADP was characterized in four of the trials reviewed for this document: #005; #007; #008; and PRISM.

#### 7.0.1a Pharmacokinetics of Tirofiban

##### Serum Concentrations in Humans

The use of a tirofiban bolus, followed by an infusion, achieved serum concentrations of tirofiban that were equivalent to steady-state levels within 30 minutes. Following discontinuation of tirofiban infusion, the plasma tirofiban concentrations decline rapidly (tables 6.1.1.12.2d.1, p. 32, and 6.1.3.12.2d.1, p. 62), reflecting its  $T_{1/2}$  of 2.1-2.2 hours in humans (table 6.1.2.12.2d.4, p. 47).

The clearance of tirofiban ( $Cl_{s-tirofiban}$  (ml/min)) was proportional to the creatinine clearance, as shown in the table below from the PRISM trial. When expressed by the fraction of the normal clearance ( $\geq 75$  ml/min), subjects with creatinine clearance rates  $< 30$  ml/min had a  $Cl_{s-tirofiban}$  of approximately 50% of normal. Note the small number of subjects with extremely diminished creatinine clearances.

Table 7.0.1a.1 (reproduces table 6.2.2.12.3.8) Tirofiban clearance during PRISM according to calculated creatinine clearance<sup>a</sup>.

	$< 30$ ml/min n=12	30-60 ml/min n=246	61-74 ml/min n=193	$\geq 75$ ml/min n=299
$Cl_{s-tirofiban}$ (ml/min)	94.98 $\pm$ 42.1	146.4 $\pm$ 67	174.99 $\pm$ 84.7	207.31 $\pm$ 86.5
$Cl_{s-tirofiban}$ (ml/min) expressed as % of $\geq 75$ ml/min Cl,	45.8%	70.5%	84.5%	--

a Data from NDA volume 1.48, ref. 9, table 16, and calculated by medical reviewer.

As a consequence of this association between creatinine and tirofiban clearance, elderly subjects, with diminished creatinine clearances, had decreased tirofiban Cl, as well.

Table 7.0.1a.2 (reproduces table 6.2.2.12.3.7) Tirofiban clearance during PRISM according to subject age<sup>a</sup>.

	565 years	$\geq 65$ years	Difference	p-value & (95% CI)
$Cl_{s-tirofiban}$ (ml/min)	195.09 $\pm$ 89	147.9 $\pm$ 65	-47.2	$< 0.001$ (-59, -35.4)

a. Data from NDA volume 1.48, ref. 9, table 1.5.

### 7.0.1a Pharmacokinetics of Tirofiban (cont)

#### Tirofiban Metabolism in Humans and Drug-Drug Interactions

Based on human liver microsomal preparations and human liver slices, the sponsor found no evidence of metabolism of tirofiban in humans (see section 4.02, p. IS).

In a sub-set of patients (n=762) in the PRISM study, the plasma clearance of tirofiban in patients receiving one of the following drugs was compared to that in patients not receiving that drugs. There were no clinically significant effect of these drugs on the plasma clearance of tirofiban: acebutolol; acetaminophen; alprazolam; amlodipine; aspirin preparations; atenolol; bromazepam; captopril; diazepam; digoxin; diltiazem; docusate sodium; enalapril; furosemide; glyburide; heparin, insulin; isosorbide; lorazepam; lovastatin; metoclopramide; metoprolol; morphine; nifedipine; nitrate preparations; oxazepam; potassium chloride; propranolol; ranitidine; simvastatin; sucralfate and temazepam. After adjusting for multiple comparisons, the only significant differences between subjects receiving/ not receiving tirofiban was for the following two drugs: levothyroxine ( $Cl_{s-tirofiban}$  175.3 ml/min without levothyroxine, 218.5 ml/min with,  $p<0.001$ ); and omeprazole (176.0 ml/min without omeprazole, 252.1 ml/min with,  $p<0.001$ ). The sponsor argues that since, in both cases, the tirofiban clearance is higher in the group taking the drug, no impact on subject safety can be expected.

The sponsor did not report the effect of tirofiban on the clearance of any of drugs.

From the data in protocol 007,008, and PRISM, the sponsor concluded that there was no effect of heparin on the dose of tirofiban required to achieve a given level of inhibition of platelet aggregation. There was, however, a significant interaction of heparin and tirofiban on bleeding time (see below).

The sponsor reported that race and gender had no effect on tirofiban clearance (see PRISM trial, tables 6.2.2.12.3.9 and 6.2.2.12.3.10, p. 123).

### 7.0.1b Pharmacodynamics of Tirofiban

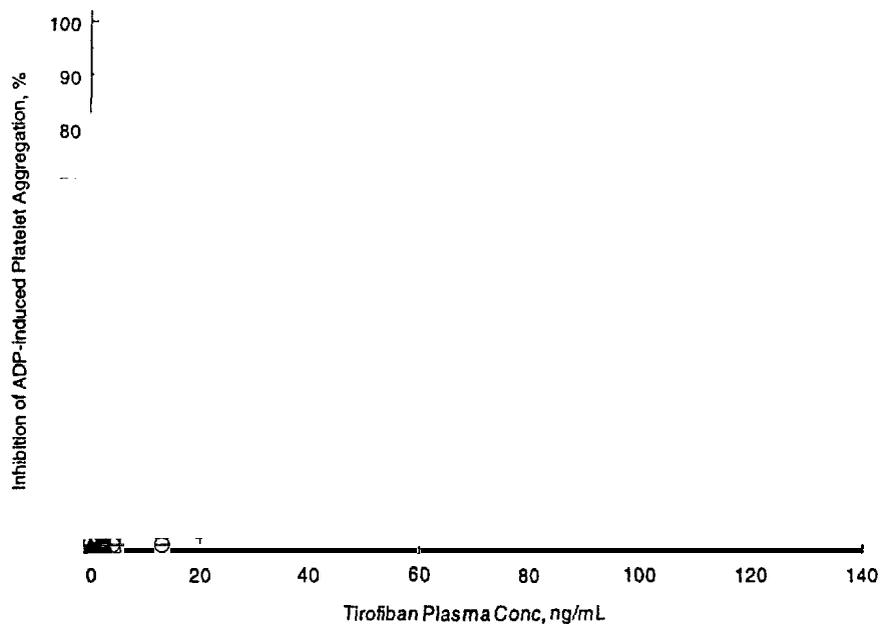
#### Inhibition of platelet aggregation

Across all studies there was a consistent, dose-dependent effect on the inhibition of platelet aggregation in response to ADP (IPA). The two doses of tirofiban used in the PRISM and PRISM-PLUS trials achieved 270% IPA in >80% of the subjects after 24 and 48 hours in protocol 008 (tables 6.1.2.12.2d.6, p. 48, and 6.1.3.12.2d.6, p. 64 from protocols 007 and OOS), an effect which was independent of the use of heparin (table 6.1.3.12.2d.7, p. 64). The high-dose tirofiban (0.6µg/kg bolus then 0.15 µg/kg/min infusion) was more effective at achieving >70% IPA than the lower-dose (0.4/0.10).

The sponsor modeled the relationship between dose and IPA in protocol 007 (section 6.1.2.12.2d) and protocol 008 (section 6.1.3.12.2d, p. 64), performed in the presence of heparin. The fitted  $C_{50}$  value of the pooled data was 12.2 ng/ml (M.9 SE), and the Hill coefficient was 1.25 ( $\pm 0.07$  SE). Data from this study compared quite well to historical data obtained from similar patients given MK-0383 without heparin (protocol #005), where the  $C_{50}$  value and the Hill coefficient values based on pooled data from the unstable angina patients without heparin were 15.5 ng/ml and 1.84, respectively. This suggests that heparin had no major effect on the relation between plasma concentration of MK-0383 and IPA in tirofiban-treated subjects. The curve below summarizes the dose-IPA curve for the entire database. It suggests that the dose of tirofiban chosen for the infusion (0.10-0.15 µg/kg/min) is on the 'flat' portion of the curve, and so relatively less-responsive to small changes in plasma tirofiban concentrations.

## 7.0.1b Pharmacodynamics of Tirofiban (cont)

Figure 7.0. 1b.1 Concentration/IPA relationship for Tirofiban vs. IPA across all Phase II-III studies,



Panel 1: 0.3  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.075  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\square$ ),  
 Panel 2: 0.4  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.1  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\circ$ ),  
 Panel 3: 0.6  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.15  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\blacktriangle$ )  
 Solid line is the fitted curve to the sigmoid- $E_{\text{max}}$  model

### Effect of Tirofiban on Template Bleedine Times

The effect of tirofiban on bleeding times at the end of 24 and 48 hours was also examined in protocols 005 and 008. Bleeding times were consistently prolonged in the tirofiban group, relative to the heparin group (see table 6.1.3.12.2d.8, p. 64). The table below shows that the addition of heparin to tirofiban had the effect of substantially increasing the number of subjects with bleeding times >30 minutes, especially the higher dose of tirofiban. The consequences of this extension of bleeding time during co-administration of tirofiban and heparin may be an increased risk of clinical bleeding. The sponsor decreased the rate of tirofiban infusion in the PRISM-PLUS trial to 0.10  $\mu\text{g}/\text{kg}/\text{min}$  for the tirofiban +heparin group (see Appendix 8, section 20.0, p. 364).

Table 7.0.1b.4 (reproduces table 6.1.3.12.2d.11) Comparison of bleeding time and bleeding time extension (BTE) from protocols #005 and #008<sup>a</sup>.

Tirofiban regimen	Tirofiban 0.4/0.1		Tirofiban 0.6/0.15	
	24 hrs	48 hrs	24 hrs	48 hrs
<b>Bleeding Time</b>				
With Heparin (#008)	14.0	20.0	25.7	30.0
Without Heparin (#005)	9.8	13.0	19.8	15.4
<b>BTE</b>				
With Heparin (#008)	2.8	2.9	2.5	4.4
Without Heparin (#005)	2.2	2.6	3.9	3.3
<b>% Subjects &gt;30 mins</b>				
With Heparin (#008)	26.3%	29.4%	50.0%	58.3%
Without Heparin (#005)	9.1%	19.1%	20.0%	23.5%

a. Data from protocols #008 and #005.

**7.0.1c Effect of Tirofiban on Clot Formation and Restenosis**

Effect of Tirofiban on clot formation in the PRISM-PLUS trial

A tertiary endpoint of the PRISM-PLUS trial was the extent of angiographically apparent thrombus detected at the time of the protocol-specified angiogram (between 48 and 96 hours after entry into study and start of study drug).

First, looking at the maximal extent of thrombus, subjects in the tirofiban +heparin group had significantly less thrombus than the heparin alone group (odds reduction 23%, p=0.022). The percentage of subjects with no detectable thrombus was also higher in the combination group (55.6% vs. 50.5% in the heparin group). The incidence of severe thrombus (grades 4 and 5) was also lower in the combination group (5.7% vs. 8.3% in the heparin group) (see table 6.2.1.12.3.8, p. 91).

The second endpoint of this study was the TIM1 flow past the culprit lesion (measured on a four point scale). Among the subjects with evaluable data, the flow was significantly greater in the tirofiban +heparin group than in the heparin group. Flow was significantly improved in the tirofiban +heparin group, compared with the heparin group (odds reduction 35%, p=0.002. Fewer of the combination group had diminished flow (TIMI grades 0,1,or 2) (18.1%) compared with the heparin group (25.5%) (see table 6.2.1.12.3.9, p. 9 1).

The third endpoint was the change in the mean diameter of the stenosis (reflecting both clot and plaque). The subjects in the combination group had a slightly smaller mean diameter than did the heparin group (76% vs. 74.7%, p=0.037 per sponsor’s analysis).

Effect of Tirofiban on restenosis in the RESTORE trial

In the RESTORE trial, the sponsor collected 211 subjects in the tirofiban arm and 205 subjects in the placebo arm who had baseline coronary angiography (followed by PTCA) and follow-up angiography after approximately 6 months. The results of these angiograms were then analyzed for evidence of an effect of tirofiban on the rate of restenosis. The treatment groups were similar in their vessel reference diameter (2.78mm in tirofiban, 2.70mm in placebo), and in the initial minimal lumen diameter (0.57mm for the tirofiban group, 0.53mm in placebo). The final lumen diameter post-PTCA was also similar (1.89mm in both groups). The table below shows the results from the three ways used by the sponsor to measure efficacy of tirofiban to slow restenosis. No significant differences in the incidence rates were detected.

Table 6.2.3.12.3.2 Repeat angiogram results from the RESTORE trial”.

	<b>Tirofiban (n=1071)</b>	<b>Placebo (n=1070)</b>	<b>p value</b>
<b>Loss of 250% of lumen diameter gain after initial PTCA</b>	105/211 (40%)	103/205 (50%)	0.99
<b>&lt;50% stenosis at follow-up<sup>c</sup></b>	100/196 (51%)	110/193 (57%)	0.26
<b>Loss of lumen diameter ≥0.72mm</b>	88/211 (42%)	90/205 (44%)	0.69

a. Data from NDA volume 1.55, page 1083 1. Shown as n (%).

b. p values calculated using chi square.

c. Subset of subjects with <50% stenosis after initial PTCA.

7.0.2 Effect of Tirofiban on Pre-Specified Endpoints

7.0.2a Effect of Tirofiban on Pre-Specified Primary and Secondary Endpoints

PRISM-PLUS

The pre-specified, primary endpoint of the PRISM-PLUS trial was the incidence of refractory cardiac ischemia, new myocardial infarction, or death from any cause within 7 days of the start of study drug. The secondary endpoints were the combined endpoint at the end of 48 hours and 30 days. The table below summarizes the incidence of this endpoint at 48, 7, 30, and 180 days.

After 7 days, subjects in the tirofiban +heparin arm had a significantly lower incidence of the primary endpoint when compared with subjects in the heparin alone group (odds ratio 0.660, p=0.004). This represented an absolute reduction of 5% in the incidence of the combined primary endpoint (17.9% vs. 12.9%).

Table 7.0.2a.1 Incidence of the primary endpoint (RIC/MI/Death) and its components at 48 hours, 7, 30, and 180 days in the PRISM-PLUS trial<sup>a</sup>.

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	Odds ratio & 95% CI <sup>e</sup>	p value (T+H vs H) <sup>b</sup>
<b>Composite endpoint at 48 hours<sup>d</sup></b> (specified secondary endpoint)	26 (7.5%)	44 (5.7%)	62 (7.8%)	<b>0.692</b> 0.462, 1.034	0.073
<b>Composite endpoint at 7 days</b> (specified primary endpoint)	59 (17.1%)	100 (12.9%)	143 (17.9%)	<b>0.660</b> <b>0.499, 0.874</b>	<b>0.004</b>
Composite endpoint at 30 days (specified secondary endpoint)	81 (23.5%)	143 (18.5%)	178 (22.3%)	<b>0.769</b> 0.599, 0.987	0.039
Composite endpoint at 180 days	105 (30.4%)	214 (27.7%)	256 (32.1%)	<b>0.811</b> 0.677, 0.973	0.024

a. Data from NDA 20-912, volume 1.42, tables 17-20 and volume 1.59, reference 55, table 1. Intent-to-treat population is used.

b. p value per sponsor using logistic regression analysis, comparing heparin(H) vs combination (T +H). Confirmed by FDA analysis. The 180 day result used a separate Cox proportional hazards model.

c. RIC: refractory ischemic conditions included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention **within 12 hours** of symptom onset.

d. The primary efficacy endpoint of the trial was the composite occurrence of refractory ischemic conditions, new myocardial infarction, or death within 7 days of start of study drug.

e. Odds ratio shown in bold.

PRISM Trial

The primary endpoint of the PRISM trial was the incidence of refractory ischemia (RI), new myocardial infarction or death at 48 hours of study drug infusion. The incidence of the same endpoint at 7 and 30 days were pre-specified secondary and supportive endpoints respectively. The table below summarizes the results for these three endpoints. Also included are the odds ratio (shown in bold) with its 95% confidence interval (CI) and the p value (verified by the FDA). For the primary endpoint, there was a significant difference between the tirofiban and heparin groups, favoring tirofiban (odds ratio 0.659, risk reduction 33%, p=0.014). After 7 and 30 days, the difference between the two groups was not significant.

Table 7.0.2a.2 incidence of the primary endpoint at 48 hours, 7 and 30 days in the PRISM trial<sup>a</sup>. The pre-specified, primary endpoint is shaded.

	Tirofiban n=1616	Heparin n=1616	Odds ratio (bold) & 95% CI	p value <sup>b</sup>
<b>Combined endpoint at 48 hours</b> (primary endpoint)	61 (3.8%)	91 (5.6%)	<b>0.659</b> 0.473, 0.919	0.014
Combined endpoint at 7 days	166 (10.3%)	182 (11.3%)	<b>0.903</b> 0.722, 1.130	0.37
Combined endpoint at 30 days	257 (15.9%)	276 (17.1%)	<b>0.919</b> 0.763, 1.108	0.38

a. Data from NDA 20-912, volume 1.48, tables 20-25. Intent-to-treat population is used, confirmed by FDA analysis.

b. p value per the sponsor based on logistic regression analysis.

c. RI: refractory cardiac ischemia. These included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, or (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes.

## 7.0.2a Effect of Tirofiban on Pre-Specified Primary and Secondary Endpoints (cont)

### RESTORE Trial

The primary endpoint in the RESTORE trial was the incidence of the following during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedure failure. The results for the primary endpoint are shown in the table below. The proportions of patients who met the composite endpoint by **30** days was 110/1071 (10.3%) in the tirofiban (+heparin) group and 130/1070 (12.2%) in the placebo (+heparin) group. This non-significant difference ( $p=0.169$ ) has an odds ratio of 0.828, which represents a 17% risk reduction for an event for the tirofiban (+heparin) group. The same combined endpoint was nominally significant at earlier time-points (48 hours and 7 days), but not at the later, pre-specified secondary endpoint (180 days).

Table 7.0.2a.3 Incidence of the combined endpoint at 48 hours, 7, 30, and 180 days in the RESTORE trial<sup>a</sup>. The pre-specified, primary endpoint is shaded.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	Odds Ratio (bold) & 95% CI	p value <sup>b</sup>
Combined endpoint at 48 hours <sup>d</sup>	58 (5.4%)	93 (8.7%)	<b>0.598</b> 0.425, 0.840	0.003
Combined endpoint at 7 days	81 (7.6%)	111 (10.4%)	<b>0.704</b> 0.522, 0.951	0.022
<b>Combined endpoint at 30 days (primary endpoint)</b>	110 (10.3%)	130 (12.2%)	<b>0.828</b> 0.632, 1.084	0.169
<b>Combined endpoint at 180 days (secondary endpoint)</b>	258 (24.1%)	290 (27.1%)	<b>0.853</b> 0.702, 1.037	0.110

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used, and confirmed by FDA analysis.

b. p value per the sponsor based on logistic regression analysis.

c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated.

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a stent because of procedural failure.

## 7.0.2b Effect of Tirofiban on Components of the Primary Endpoint

### PRISM-PLUS

The table below summarizes the incidence of the components of the primary endpoint at 48, 7, 30, and 180 days. The secondary endpoints for the PRISM-PLUS trial were the composite endpoint (RIC, MI, Death) at 48 hours and 30 days. At 30 days, the tirofiban +heparin group had a significantly lower incidence of the combined endpoint when compared with heparin only, whereas at 48 hours, the significance was marginal ( $p=0.073$ ). For the components of the primary endpoint, no significant effect of tirofiban +heparin on the incidence of death was detected at any time up to 180 days after enrollment, although a trend towards benefit exists for many components. A significant effect on RIC was seen after 7 days, and on recurrent MI (fatal and non-fatal) after 7 and 30 days. There was a nominally significant effect of tirofiban +heparin on the incidence of MI/Death at the end of 48 hours, 7 and 30 days.

### 7.0.2b Effect of Tirofiban on Components of the Primary Endpoint

Table 7.0.2b.1 Incidence of components of the primary endpoint (RIC, MI, Death) after 48 hours, 7, 30, and 180 days in the PRISM-PLUS trial<sup>a</sup>.

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	Odds ratio & 95% CI <sup>e</sup>	p value (T+H vs H) <sup>b</sup>
MI/Death at 48 hours	6 (1.7%)	7 (0.9%)	21 (2.6%)	<b>0.330</b> 0.139, 0.783	0.012
MI/Death at 7 days	36 (10.4%)	38 (4.9%)	66 (8.3%)	<b>0.565</b> 0.374, 0.854	0.007
MI/Death at 30 days	47 (13.6%)	67 (8.7%)	95 (11.9%)	<b>0.695</b> 0.499, 0.967	0.031
MI/Death at 180 days	55 (15.9%)	95 (12.3%)	122 (15.3%)	<b>0.775</b> 0.593, 1.014	0.063
RIC at 48 hours	23 (6.7%)	37 (4.8%)	47 (5.9%)	<b>0.774</b> 0.496, 1.209	0.26
RIC at 7 days	39 (11.3%)	72 (9.3%)	101 (12.7%)	<b>0.685</b> 0.495, 0.946	0.022
RIC at 30 days <sup>f</sup>	44 (12.8%)	82 (10.6%)	107 (13.4%)	<b>0.741</b> 0.543, 1.010	0.058
RIC at 180 days <sup>f</sup>	44 (12.8%)	82 (10.6%)	107 (13.4%)	<b>0.755</b> 0.566, 1.007	0.056
MI (both fatal and non-fatal) at 48 hours	5 (1.4%)	6 (0.8%)	19 (2.4%)	<b>0.313</b> 0.124, 0.790	0.014
MI (both fatal and non-fatal) at 7 days	24 (7.0%)	30 (3.9%)	56 (7.0%)	<b>0.528</b> 0.335, 0.833	0.006
MI (both fatal and non-fatal) at 30 days	31 (9.0%)	51 (6.6%)	73 (9.2%)	<b>0.696</b> 0.479, 1.010	0.057
MI (both fatal and non-fatal) at 180 days	35 (10.1%)	64 (8.3%)	84 (10.5%)	<b>0.761</b> 0.549, 1.053	0.100
Death at 48 hours	2 (0.6%)	1 (0.1%)	2 (0.2%)	<b>0.509</b> 0.046, 5.634	0.58
Death at 7 days	16 (4.6%)	15 (1.9%)	15 (1.9%)	<b>1.010</b> 0.489, 2.086	0.98
Death at 30 days	21 (6.1%)	28 (3.6%)	36 (4.5%)	<b>0.784</b> 0.473, 1.301	0.35
Death at 180 days	25 (7.2%)	53 (6.9%)	56 (7.0%)	<b>0.965</b> 0.663, 1.406	0.85

a. Data from NDA 20-912 Aggrastat<sup>®</sup> Clinical Study Report, Volume 1, Table 1. Intention-to-treat population is used, confirmed by FDA analysis.

b. p value per sponsor using logistic regression analysis, comparing heparin(H) vs combination (T +H). The 180 day result used a separate Cox proportional hazards model.

c. RIC: refractory ischemic conditions included:- (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention within 12 hours of symptom onset.

d. The primary efficacy endpoint of the trial was the composite occurrence of refractory ischemic conditions, new myocardial infarction, or death within 7 days of start of study drug.

e. Odds ratio shown in bold.

f. The incidence of RIC was the same at 30 and 180 days, because the subjects experiencing recurrent anginal events were classified as recurrent UAP, not RIC, after hospital discharge (per protocol).

## 7.0.2b Effect of Tirofiban on Components of the Primary Endpoint (cont)

### PRISM Trial

The table below summarizes the results from analyses on the incidences of various components of the combined primary endpoint from PRISM trial. While there is a trend favoring the tirofiban group in many of the components, after 48 hours the only nominally significant effect was on mortality at 30 days (but not 48 hours or 7 days).

6.2.2.12.2d.1 Incidence of components of the primary endpoint at 48 hours, 7 and 30 days in the PRISM trial<sup>d</sup>

	<b>Tirofiban n=1616</b>	<b>Heparin n=1616</b>	<b>Odds ratio (bold) &amp; 95% CI</b>	<b>p value<sup>b</sup></b>
<b>MI/ Death at 48 hours</b>	<b>19 (1.2%)</b>	<b>25 (1.5%)</b>	<b>0.761</b> 0.417, 1.389	<b>0.37</b>
<b>MI/ Death at 7 days</b>	<b>53 (3.3%)</b>	<b>68 (4.2%)</b>	<b>0.770</b> 0.534, 1.111	<b>0.16</b>
<b>MI/Death at 30 days</b>	<b>93 (5.8%)</b>	<b>115 (7.1%)</b>	<b>0.795</b> 0.599, 1.056	0.11
<b>RI at 48 hours<sup>c</sup></b>	<b>56 (3.5%)</b>	<b>86 (5.3%)</b>	<b>0.640</b> 0.453, 0.903	0.011
<b>RI at 7 days</b>	<b>147 (9.1%)</b>	<b>160 (9.9%)</b>	<b>0.913</b> 0.721, 1.156	<b>0.45</b>
<b>RI at 30 days</b>	<b>172 (10.6%)</b>	<b>174 (10.8%)</b>	<b>0.992</b> 0.793, 1.241	<b>0.94</b>
<b>MI (both fatal and non-fatal) at 48 hours</b>	<b>14 (0.9%)</b>	<b>22 (1.4%)</b>	<b>0.639</b> 0.325, 1.254	<b>0.19</b>
<b>MI (both fatal and non-fatal) at 7 days</b>	<b>42 (2.6%)</b>	<b>50 (3.1%)</b>	<b>0.837</b> 0.552, 1.270	<b>0.40</b>
<b>MI (both fatal and non-fatal) at 30 days</b>	<b>66 (4.1%)</b>	<b>69 (4.3%)</b>	<b>0.957</b> 0.677, 1.352	<b>0.80</b>
<b>Death at 48 hours</b>	<b>6 (0.4%)</b>	<b>4 (0.2%)</b>	<b>1.488</b> 0.419, 5.289	<b>0.54</b>
<b>Death at 7 days</b>	<b>16 (1.0%)</b>	<b>25 (1.6%)</b>	<b>0.630</b> 0.335, 1.185	<b>0.15</b>
<b>Death at 30 days</b>	<b>37 (2.3%)</b>	<b>59 (3.6%)</b>	<b>0.612</b> 0.403, 0.930	<b>0.021</b>

a. Data from NDA 20-912, volume 1.48, tables -25. Intent-to-treat population is used, confirmed by FDA analysis

b. p value per the sponsor based on logistic regression analysis

c. RI: refractory cardiac ischemia. These included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, or (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes.

**7.0.2b Effect of Tirofiban on Components of the Primary Endpoint (cont)**  
**RESTORE Trial**

The difference between treatments in the individual components of the composite were all in the same direction, favoring tirofiban, except for death, which was rare and appeared to occur equally in the two groups. through the end of 7 days, there was a nominally significant effect of tirofiban to reduce the incidence of CABG and repeat PTCA, which did not persist through 30 days.

Table 6.2.3.12.2d.1 Incidence of the combined endpoint and its components at 48 hours, 7, 30, and 180 days in the RESTORE trial<sup>a</sup>.

	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	Odds Ratio (bold) & 95% CI	p value <sup>b</sup>
<b>CABG at 48 hours</b>	10 (0.9%)	15 (1.4%)	<b>0.653</b> 0.291, 1.461	0.299
<b>CABG at 7 days</b>	13 (1.2%)	17 (1.6%)	<b>0.748</b> 0.402, 1.139	0.436
<b>CABG at 30 days</b>	20 (1.9%)	23 (2.2%)	<b>0.859</b> 0.469, 1.575	0.623
<b>CABG at 180 days</b>	59 (5.5%)	73 (6.8%)	<b>0.793</b> 0.556, 1.130	0.199
<b>Repeat PTCA at 48 hours<sup>f</sup></b>	12 (1.1%)	34 (3.2%)	<b>0.343</b> 0.176, 0.666	0.002
<b>Repeat PTCA at 7 days</b>	29 (2.7%)	47 (4.4%)	<b>0.603</b> 0.377, 0.967	0.036
<b>Repeat PTCA at 30 days</b>	45 (4.2%)	58 (5.4%)	<b>0.766</b> 0.514, 1.142	0.191
<b>Repeat PTCA at 180 days</b>	168 (15.7%)	183 (17.1%)	<b>0.902</b> 0.717, 1.135	0.378
<b>Stent placement at 48 hours<sup>e</sup></b>	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.096	0.094
<b>Stent placement at 7 days</b>	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.095	0.094
<b>Stent placement at 30 days</b>	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.096	0.094
<b>Stent placement at 180 days</b>	16 (1.5%)	27 (2.5%)	<b>0.586</b> 0.314, 1.095	0.094
<b>MI (fatal &amp; non-fatal) at 48 hours</b>	29 (2.7%)	47 (4.4%)	<b>0.599</b> 0.373, 0.960	0.033
<b>MI (fatal &amp; non-fatal) at 7 days</b>	39 (3.6%)	57 (5.3%)	<b>0.665</b> 0.438, 1.010	0.055
<b>MI (fatal &amp; non-fatal) at 30 days</b>	45 (4.2%)	61 (5.7%)	<b>0.720</b> 0.485, 1.069	0.104
<b>MI (fatal &amp; non-fatal) at 180 days</b>	67 (6.3%)	81 (7.6%)	<b>0.809</b> 0.578, 1.132	0.216
<b>Death at 48 hours</b>	2 (0.2%)	2 (0.2%)	<b>0.974</b> 0.136, 6.953	0.979
<b>Death at 7 days</b>	4 (0.4%)	4 (0.4%)	<b>0.988</b> 0.246, 3.964	0.986
<b>Death at 30 days</b>	9 (0.8%)	8 (0.7%)	<b>1.126</b> <b>0.433, 2.930</b>	0.808
<b>Death at 180 days</b>	19 (1.8%)	15 (1.4%)	<b>1.274</b> <b>0.644, 2.521</b>	<b>0.487</b>

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used, and confirmed by FDA analysis.

b. p value per the sponsor based on logistic regression analysis.

c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a stent because of procedural failure.

e. Stent placement refers to those stents placed after the initial PTCA for procedure failure.

f. Includes both PTCA and atherectomy.

### 7.0.2c Analysis of the primary endpoint and selected other endpoints using Pearson's chi-square analysis.

The FDA performed a post-hoc analysis of the primary endpoint and its components using Pearson's chi square analysis, and the results are shown below.

#### PRISM-PLUS Trial

Table 7.0.2c.1 (from 6.2.1.12.3.1) Incidence of the combined endpoint (RIC/MI/Death) and MI/ Death at 48 hours, 7, 30, and 180 days in the PRISM-PLUS trial analyzed for significance using chi square<sup>a,c,d</sup>.

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	p value by chi square (T+H vs H) <sup>b</sup>
Composite endpoint at 48 hours <sup>d</sup> (specified secondary endpoint)	26 (7.5%)	44 (5.7%)	62 (7.8%)	0.099
Composite endpoint at 7 days (specified primary endpoint)	59 (17.1%)	100 (12.9%)	143 (17.9%)	0.006
Composite endpoint at 30 days (specified secondary endpoint)	81 (23.5%)	143 (18.5%)	178 (22.3%)	0.060
Composite endpoint at 180 days	105 (30.4%)	214 (27.7%)	256 (32.1%)	0.055
MI/Death at 48 hours	6 (1.7%)	7 (0.9%)	21 (2.6%)	0.010
MI/Death at 7 days	36 (10.4%)	38 (4.9%)	66 (8.3%)	0.007
MI/Death at 30 days	47 (13.6%)	67 (8.7%)	95 (11.9%)	0.034
MI/Death at 180 days	55 (15.9%)	95 (12.3%)	122 (15.3%)	0.083

a. Data from NDA 20-912, volume 1.42, tables 17-20 and volume 1.59, reference 55, table 1. Intent-to-treat population is used.

b. p value using Pearson's chi square by FDA analysis.

c. FUC: refractory ischemic conditions included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on ECG despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic ECG changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention within 12 hours of symptom onset.

d. The primary efficacy endpoint of the trial was the composite occurrence of refractory ischemic conditions, new myocardial infarction, or death within 7 days of start of study drug.

#### PRISM Trial

Table 7.0.2c.2 (from table 6.2.2.12.2d.2) Incidence of the combined endpoint and Death/ MI at 48 hours, 7 and 30 days in the PRISM trial, analyzed using chi square<sup>a</sup>. The primary endpoint is shaded.

	Tirofiban n=1616	Heparin n=1616	p value by chi square <sup>b</sup>
Combined endpoint at 48 hours (primary endpoint)	61 (3.8%)	91 (5.6%)	0.0127
Combined endpoint at 7 days	166 (10.3%)	182 (11.3%)	0.36
Combined endpoint at 30 days	257 (15.9%)	276 (17.1%)	0.37
MI/Death at 48 hours	19 (1.2%)	25 (1.5%)	0.37
MI/Death at 7 days	53 (3.3%)	68 (4.2%)	0.17
MI/Death at 30 days	93 (5.8%)	115 (7.1%)	0.12

a. Data from NDA 20-912, volume 1.48, tables 20-25. Intent-to-treat population is used.

b. p value per the FDA based using Pearson's chi square.

c. RI: refractory cardiac ischemia. These included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on ECG despite optimal medical therapy, or (2) hemodynamic instability in the setting of recurrent angina or ischemic ECG changes.

#### RESTORE

Table 7.0.2c.3 (from table 6.2.3.12.2d.2) Incidence of the combined endpoint at 48 hours, 7, 30, and 180 days in the RESTORE trial, analyzed using chi square<sup>a</sup>. The primary endpoint is shaded.

Clinical endpoint	Tirofiban <sup>c</sup> n=1071	Placebo <sup>c</sup> n=1070	p value by chi square <sup>b</sup>
Combined endpoint at 48 hours <sup>d</sup>	58 (5.4%)	93 (8.7%)	0.003
Combined endpoint at 7 days	81 (7.6%)	111 (10.4%)	0.023
Combined endpoint at 30 days (primary endpoint)	110 (10.3%)	130 (12.2%)	0.168
Combined endpoint at 180 days (secondary endpoint)	258 (24.1%)	290 (27.1%)	0.110

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used.

b. p value per the FDA using Pearson's chi square.

c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated.

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of stent because of procedural failure.

### 7.0.3 Sub-group and Post-hoc Analyses

#### 7.0.3.1 Analyses in the PTCA subgroup of the UAP/ NQWMI population (RESTORE trial)

The sponsor noted that the pivotal p-value for the RESTORE trial is  $>0.05$  (see table 6.2.3.12.2d.1), raising a question about the clinical benefit of tirofiban +heparin in the post-PTCA population (compared with heparin alone). In an effort to place this finding into a larger efficacy context, the sponsor performed several subgroup analyses, which have been reviewed in the respective trial summaries above. Some of these analyses, however, require some further discussion. These analyses are broken into two groups: those which were concerned primarily with the RESTORE trial; and those involving, primarily, the PRISM-PLUS and PRISM trials.

#### 7.0.3.1a Reanalysis of RESTORE trial combined endpoint using 'urgent/emergent revascularization'

The primary endpoint in the RESTORE trial, as stated above, was the occurrence of the following composite endpoint during the first 30 days: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a coronary endovascular stent because of procedural failure. After the study results were known, the sponsor raised the issue of comparability of this endpoint and endpoints used in other trials of platelet inhibitors. Specifically, they contrasted their primary endpoint, which includes 'CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia,' with the endpoints used in other trials of  $\text{P2b/3a}$  receptor antagonists, suggesting that the other trials included as endpoints only those subjects with whose PTCA or CABG was 'emergent.'

The original criteria for endpoint determination, which were sent to the investigators are shown below, taken from the Endpoint Committee Manual.

##### Coronary Artery Bypass Grafting (CABG)

CABG performed due to complications (e.g., large dissection, perforation) or failure of the initial PTCA/ atherectomy attempt, or due to recurrent ischemia following completion of the initial PTCA/ atherectomy.

##### Repeat Percutaneous Intervention for Recurrent Ischemia

Subsequent revascularization (i.e., after completion of the initial PTCA/ atherectomy) of the same vessel dilated at the initial procedure, including PTCA/ atherectomy and intracoronary stent insertion for recurrent ischemia.

Per the sponsor, recurrent ischemia was generally evidenced by a recurrent clinical ischemic event (e.g., angina, MI) or provocative testing (e.g., stress testing) and was denoted by the investigators on the CRF. This form, in addition to other supportive documents (such as lab sheets for CPK-MB) were provided to the Endpoint Adjudication Committee members for adjudication of endpoints.

After the initial analysis was performed, the sponsor performed a post-hoc analysis in which the composite endpoint was redefined to include CABG or revascularizations (for original target or non-target vessel) for urgent or emergent indications only. For the blinded re-adjudication or revascularization endpoints in this post-hoc analysis, a letter was sent outlining new criteria for determining whether or not the procedure was done on an urgent/emergent basis. In general, this was defined as a procedure that required a 'rush' to the catheterization laboratory or for a procedure that could not have been performed on an elective basis (e.g., not wait 24 hours).

The results of this post-hoc analysis, including only emergency angioplasty or bypass surgery as components of the endpoints, adjudicated by the Endpoint Committee, are shown in the table below. This analysis was based on 67/103 of the PTCAs (65%) and 27/43 (63%) of the CABGs that were determined to be urgent/emergent by the above criteria. The 30-day event rates for the combined endpoint using only 'emergency CABG/ PTCA were 10.5% for the placebo group and 8.0% for the tirofiban group (post-hoc analysis,  $p=0.052$ ). In addition, the rates of emergency PTCA were 4.0% in the placebo group and 2.3% in the tirofiban group (post-hoc analysis,  $p=0.027$ ). There was no difference in the rates of emergency CABG between the tirofiban and placebo groups.

Results at Days 2 and 7 were similar to those using the protocol definition of the composite (including 'non-urgent/emergent revascularization'). The sponsor suggested that this is because PTCAs and CABGs that occurred early were more likely to be emergency or urgent procedures.

### 7.0.3.1a Reanalysis of RESTORE trial combined endpoint using ‘urgent/emergent revascularization’ (cont)

Table 7.0.3.1a.1 (from table 6.2.3.12.3.4) ‘Primary endpoint’ including only urgent/emergent revascularization procedures from the RESTORE trial”.

	Tirofiban n=1071	Placebo n=1070	95% Confidence Intervals	pvalue <sup>b</sup>
Combined endpoint at 48 hours	56 (5.2%)	93 (8.7%)	0.490, 0.813	<b>0.002</b>
Combined endpoint at 7 days	74 (6.9%)	105 (9.8%)	0.499, 0.928	<b>0.015</b>
Combined endpoint at 30 days	86 (8.0%)	112 (10.5%)	0.556, 1.003	<b>0.052</b>
Emergency CABG at 48 hours	10 (0.9%)	14 (1.3%)	0.311, 1.595	<b>0.422</b>
Emergency CABG at 7 days	12 (1.1%)	15 (1.4%)	0.366, 1.690	<b>0.539</b>
Emergency CABG at 30 days	12 (1.1%)	15 (1.4%)	0.366, 1.690	<b>0.539</b>
Emergency repeat PTCA at 48 hours	10 (0.9%)	35 (3.3%)	0.136, 0.561	<b>co.00 1</b>
Emergency repeat PTCA at 7 days	22 (2.1%)	42 (3.9%)	0.303, 0.863	<b>0.012</b>
Emergency repeat PTCA at 30 days	25 (2.3%)	43 (4.0%)	0.345, 0.938	<b>0.027</b>
Stent placement at 48 hours	16 (1.5%)	27 (2.5%)	0.314, 1.096	0.094
Stent placement at 7 days	16 (1.5%)	27 (2.5%)	0.314, 1.095	<b>0.094</b>
Stent placement at 30 days	16 (1.5%)	27 (2.5%)	0.314, 1.096	<b>0.094</b>
MI (both fatal and non-fatal) at 48 hours	29 (2.7%)	47 (4.4%)	0.373, 0.960	<b>0.033</b>
MI (both fatal and non-fatal) at 7 days	39 (3.6%)	57 (5.3%)	0.438, 1.010	<b>0.055</b>
MI (both fatal and non-fatal) at 30 days	45 (4.2%)	61 (5.7%)	0.485, 1.069	<b>0.104</b>
Death at 48 hours	2 (0.2%)	2 (0.2%)	0.136, 6.953	<b>0.979</b>
Death at 7 days	4 (0.4%)	4 (0.4%)	0.246, 3.964	<b>0.986</b>
Death at 30 days	9 (0.8%)	8 (0.7%)	0.433, 2.930	<b>0.808</b>

a. Data from NDA volume 1.55, ref. 11, table 22 and electronic datasets. Shown as n (%).

b. post-hoc analysis p value **calculated** using chi square analysis. No adjustment made for post-hoc analysis or multiplicity.

### 7.0.3.1b Comparison of the language used in the primary endpoints for the RESTORE trial and other platelet-inhibitors trials in the post-PTCA sub-group of UAP/NQWMI

The next section compares the primary endpoints from other trials of IIb/IIIa receptor antagonists. A summary of the efficacy of these trials can be found in appendix 7, section 19.0. The sponsor contrasted the language regarding the inclusion of subjects with recurrent ischemia in the trials involving subjects post-PTCA with the primary endpoint of the RESTORE trial. Key words have been underlined by the medical reviewer for emphasis.

#### Primary endpoint for the RESTORE trial

1. The incidence of adverse cardiac outcomes (a prespecified composite of any of the following clinical events: death from any cause, nonfatal myocardial infarction, coronary artery bypass grafting [CABG] or repeat percutaneous intervention for recurrent ischemia, or insertion of a coronary endovascular stent because of procedural failure) within 30 days of PTCA or atherectomy, compared to placebo (from NDA volume 1.55, ref 11, page 10766).

#### Primary endpoints and other pertinent information from other trials of IIb/IIIa receptor antagonists

1. Reopro (abciximab)

a. The CAPTURE trial primary endpoint: the occurrence, within 30 days after randomization, of death (from any cause), myocardial infarction, or and urgent intervention for treatment of recurrent ischemia (angioplasty, coronary artery bypass surgery, intracoronary stent placement, intra-aortic balloon pump). (2).

b. The EPIC trial primary endpoint: the *occurrence*, within 30 days after randomization, of death (from any cause), nonfatal myocardial infarction, coronary-artery bypass grafting or repeat percutaneous intervention for acute ischemia, and insertion of an endovascular stent because of procedural failure or placement of an intra-aortic counterpulsation balloon pump to relieve refractory ischemia( 1).

Without access to the original Investigator’s Brochure it isn’t possible to know how ‘acute ischemia’ was to have been interpreted. However, in the publication of the EPIC results, only ‘emergency PTCA’ and ‘emergency CABG’ are reported (Table 2 of (1)).

### 7.0.3.1b Comparison of the language used in the primary endpoints for the RESTORE trial and other platelet-inhibitors trials in the post-PTCA sub-group of UAP/NQWMI (cont)

#### 1. Reopro (abciximab) (cont)

c. The EPILOG trial primary endpoint: the occurrence of death (from any cause), myocardial infarction or reinfarction, or severe myocardial ischemia requiring urgent repeated coronary bypass surgery or repeated percutaneous coronary revascularization within 30 days of randomization (3).

A secondary endpoint of the EPILOG trial was the incidence of death, MI or CABG/PTCA (both urgent and non-urgent) within 6 months of randomization.

In the results of the trial (see Appendix 7, section 19.0), low-dose heparin +Abciximab had no significant effect on the incidence of the secondary endpoint, which included both urgent and non-urgent revascularization.

#### 2. Integrilin (eptifibatide)

a. IMPACT-II trial primary endpoint: the occurrence, within 30 days after randomization, of death, myocardial infarction, urgent or emergency repeat coronary intervention, urgent or emergency coronary-artery bypass surgery, or index placement of an intracoronary stent for abrupt closure(4).

b. PURSUIT trial primary endpoint: the occurrence of death and/or MI within 30 days after randomization (from Medical Officer review of PURSUIT trial, submitted as part of NDA review).

### 7.0.3.2 Analyses in UAP/NQWMI population, with and without PTCA and CABG (PRISM-PLUS and PRISM trials)

The sponsor noted that the pivotal p-value for the RESTORE trial is  $>0.05$  (see table 6.2.3.12.2d.1), raising a question about the clinical benefit of tirofiban +heparin in the post-PTCA population (compared with heparin alone). To further define the benefits of tirofiban in the post-procedure setting, they performed several analysis.

First, they analyzed the clinical outcomes in the PRISM-PLUS and PRISM trials, separating the subjects according to whether or not they received PTCA. The intent was to extract a population that resembled the RESTORE population (thus, had received PTCA). The sponsor suggests that there was evidence of benefit for tirofiban in this population, supporting the claim for the use of tirofiban in subjects undergoing PTCA.

Second, the sponsor looked at the outcome of subjects in the PRISM-PLUS trial who received PTCA or CABG, compared with those subjects who had neither procedure during the initial 30 days. This analysis allows us to ask whether there is any indication of benefit for tirofiban in the population who did not receive PTCA or CABG (a 'medical-management' group, if you will).

Third, the effects of frequency of invasive cardiac procedures in the treatment groups in the three trials are summarized.

### 7.0.3.2a Comparability of the subjects by receipt of PTCA in the PRISM-PLUS, PRISM, and RESTORE

The three populations had some important differences which need to be kept in mind while interpreting the results of this post-hoc analysis.

#### 1. Time to entry into the trial

While all three trials enrolled subjects with acute coronary syndrome, the duration of the acute coronary syndrome was up to 72 hours prior to study entry in the RESTORE trial, while it was  $\leq 12$  hours in the PRISM-PLUS trial, and  $\leq 24$  hours in the PRISM trial. This is reflected in the duration of time from onset of pain to start of study drug, which is shown below for the PRISM-PLUS and PRISM trials. No information is available as to the average duration of symptoms prior to entry into the RESTORE trial.

#### 2. Population enrolled in the trial

The demographics of the populations who got PTCA in each of the three trials are summarized in appendix 10, 22.0.1a (Baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials). Overall, PTCA subjects in the PRISM-PLUS had a higher incidence of ECG ischemia and Non-Q-Wave MI on presentation as compared to subjects undergoing PTCA enrolled in the PRISM study. In addition, the RESTORE study population included subjects presenting with ST elevation myocardial infarctions ( the primary angioplasty cohort) and Q-wave MIs; such subjects were excluded in the other trials.

#### 3. Duration, timing, and dose of study drug administration

The duration, timing, and dose of study drug administration are summarized in appendix 10, section 22.0 (Comparability of tirofiban dose in the PRISM-PLUS, PRISM, and RESTORE trials), In general, subjects in the RESTORE trial started study drug longer after their last episode angina qualifying them for entry into the study, received less overall tirofiban, and received it for a shorter period of time, when compared with PRISM-PLUS and PRISM. Subjects in the PRISM-PLUS received study drug for the longest period of time (up to 108 hours).

### 7.0.3.2b Analysis of the subjects by receipt of PTCA in the PRISM-PLUS trial

With these caveats, the sponsor undertook an analysis of those subjects in the three trials who underwent PTCA during their initial hospitalization.

In PRISM-PLUS, a total of 584 subjects had a PTCA during the initial hospitalization, 109/345 (31.6%) in the tirofiban alone group, 239/773 (30.9%) of the subjects in tirofiban +heparin group, and 236/797 (29.6%) of the heparin only group underwent PTCA during their initial hospitalization. Of these, there were 2 combination subjects who never received study drug, and 1 combination patient for whom an elapsed could not be calculated. The following data refer to the remaining 581 subjects.

The table below summarizes the data for all subjects (drawn from the primary analysis above), and those subjects who did or did not receive PTCA during their initial hospitalization, for the initial 30 day period in the following groupings:

Subjects who underwent PTCA:

- 1) Incidence rates over the entire 30-day period (from Day 1 to Day 30).
- 2) Incidence rates prior to the PTCA (from study Day 1 until the time of PTCA).
- 3) Incidence rates following PTCA through Day 30 (from the time of PTCA to Day 30).

Subjects who did not undergo PTCA during the initial hospitalization:

- 1) Incidence rates over the entire 30-day period (from Day 1 to Day 30).

These data do not include subjects with a PTCA following a hospital readmission.

The sponsor performed a post-hoc analysis looking at the incidence of clinical endpoints in the population who received a PTCA during the initial hospitalization. This analysis, in part, aims to replicate the population studied in the RESTORE trial. In that trial, subjects received tirofiban coincident with PTCA, while in this trial the two events were not necessarily linked (that is, some subjects received PTCA after finishing their study drug infusion, while for other the two occurred together). Overall 239/773 (30.9%) of the subjects who received tirofiban +heparin, and 236/797 (29.6%) of the heparin only group underwent PTCA during their initial hospitalization.

At the reviewer's request, the sponsor also summarized the incidence of clinical events prior to PTCA in the population who ultimately received them, and the event rate in the subjects who did not receive PTCA during the 30 initial 30 days. This issue is discussed at greater length in section 7.0, the integrated efficacy summary.

The table below summarizes the data for all subjects (drawn from the primary analysis above), and those subjects who did or did not receive PTCA during their initial hospitalization, for the initial 30 day period. For the subjects who received PTCA, the incidence before and after PTCA are shown. For the composite endpoint, as well as death and MI, the tirofiban +heparin group had a lower incidence of the clinical endpoints during the first 7 and 30 days after PTCA, compared with either heparin or tirofiban alone. The tirofiban +heparin group had a lower incidence of the primary endpoint compared with either tirofiban or heparin alone. Note that rates of the clinical events were also lower in the subjects who did not receive PTCA in the tirofiban +heparin group, compared with heparin alone.

### 7.0.3.2b Analysis of the subjects by receipt of PTCA in the PRISM-PLUS trial (cont)

Table 7.0.3.2b.1 (from table 6.2.1.12.3.12) Incidence of clinical events in during the first 30 days grouped according to receipt of PTCA in the PRISM-PLUS trial<sup>a,c</sup>.

Clinical endpoint	Tirofiban	Tirofiban +Heparin	Heparin
<b>Composite Endpoint (RIC, MI, Death)</b>			
All subjects	811345 (23.5%)	143/773 (18.5%)	178/797 (22.3%)
Subjects who underwent PTCA <sup>b</sup>	28/109 (25.7%)	43/239 (18.0%)	57/236 (24.2%)
Prior to PTCA only	18/109 (16.5%)	24/239 (10.0%)	30/236 (12.7%)
Subsequent to PTCA only	17/109 (15.6%)	21/239 (8.8%)	36/236 (15.2%)
Subjects who did not undergo PTCA	53/236 (22.5%)	100/534 (18.7%)	121/561 (21.6%)
<b>MI (fatal/ nonfatal)</b>			
All subjects	31/345 (9.0%)	51/773 (6.6%)	73/797 (9.2%)
Subjects who underwent PTCA <sup>b</sup>	15/109 (13.8%)	21/239 (8.8%)	29/236 (12.3%)
Prior to PTCA only	4/109 (3.7%)	7/239 (2.9%)	10/236 (4.2%)
Subsequent to PTCA only	12/109 (11.0%)	14/239 (5.9%)	20/236 (8.5%)
Subjects who did not undergo PTCA	16/236 (6.8%)	30/534 (5.6%)	44/561 (7.8%)
<b>Death</b>			
All subjects	21/345 (6.1%)	28/773 (3.6%)	36/797 (4.5%)
Subjects who underwent PTCA <sup>b</sup>	1/109 (0.9%)	2/239 (0.8%)	5/236 (2.1%)
Prior to PTCA only	0 (0%)	0 (0%)	0 (0%)
Subsequent to PTCA only	1/109 (0.9%)	2/239 (0.8%)	5/236 (2.1%)
Subjects who did not undergo PTCA	20/236 (8.5%)	26/534 (4.9%)	31/561 (5.5%)

a. Data from NDA 20-912, volume 1.42, reference 5, table 27 and adjoining text, and from personal communication with sponsor and confirmed by the FDA.

b. The pre- and post-PTCA columns are not additive, as some individuals had events both pre- and post-PTCA.

The table above summarizes clinical events that occurred during the first 30 days of after start of the study. This means that an individual who had PTCA on day 23 (for example) would have follow-up information for only an additional 7 days. The FDA performed a similar analysis looking at events that occurred during the first 7 days after PTCA, where a larger % of the subjects have data for all 7 days. This is presented only for those subjects who received PTCA, since they are the only group affected by the 30 day cut-off for follow-up (those who did not get PTCA have clinical event data for an entire 30 days). The sponsor used a Cox-Regression model to analyze the impact of PTCA and tirofiban on the clinical outcomes in this population. They reported that tirofiban +heparin significantly reduced the incidence of the primary endpoint at the end of 7 days after PTCA (risk reduction 31.6%, 95% CI 11.7% to 47%, p=0.004) in this population.

Table 7.0.3.2b.2 (from table 6.2.1.12.3.3) Incidence of clinical events in during the first 7 days following receipt of PTCA in the PRISM-PLUS trial<sup>a</sup>.

Clinical endpoint	Tirofiban n=109/345 (31.6% of total)	Tirofiban +Heparin n=239/773 (30.9% of total)	Heparin n=236/797 (29.6% of total)
Composite Endpoint (RIC, MI, Death)	12 (11.0%)	13 (5.4%)	25 (10.6%)
MI/Death	11 (10.1%)	9 (3.8%)	17 (7.2%)
MI (fatal/ nonfatal)	10 (9.2%)	9 (3.8%)	15 (6.4%)
MI (fatal)	0 (0%)	1 (0.4%)	0 (0%)
Death	1 (0.9%)	1 (0.4%)	2 (0.9%)

a. Data from electronic datasets and SAS analysis per FDA.

### 7.0.3.2b Analysis of the PRISM-PLUS trial populations who underwent PTCA (cont)

Within the group of subjects in the PRISM-PLUS trial who underwent PTCA, a smaller subgroup had PTCA during study drug infusion (19.7% of all subjects in the tirofiban group, 19.9% in the tirofiban +heparin, 21.8% of the heparin group). The table below summarizes the three populations: those who received PTCA; those who received PTCA during drug infusion; and the same population expressed as a fraction of only those subjects who received PTCA.

Table 7.0.3.2b.3 PRISM-PLUS subjects who received PTCA<sup>a</sup>.

Population	Tirofiban	Tirofiban +Heparin	Heparin
Subjects who received PTCA	109/345 (31.6%)	239/773 (30.9%)	236/797 (29.6%)
Subjects who received PTCA during study drug infusion	68/345 (19.7%)	154/773 (19.9%)	174/797 (21.8%)
Fraction of only the subjects who received PTCA who received it during study drug infusion	68/109 (62.3%)	154/239 (64.4%)	174/236 (73.7%)

a. Data from sponsor at request of medical reviewer.

The table below is an analysis of the clinical event incidence for all PRISM-PLUS subjects who underwent PTCA while on study drug during the initial hospitalization. Note that the overall event rates are low, when compared with the entire PRISM-PLUS trial population (see table 6.2.1.12.3.13 above, p. 93). This may be, in part, due to shortened follow-up, as only endpoints that occurred from the time of PTCA until day 30 of the study are included in the analysis below.

Table 7.0.3.2b.4 Incidence of clinical events subsequent to PTCA in PRISM-PLUS subjects who underwent PTCA while on study drug<sup>a</sup>.

Endpoint	Tirofiban Alone (N=68)	Tirofiban + Heparin (N=154)	Heparin Alone (N=174)
Composite (Death, MI, RIC)	13 (19.1%)	17 (11.0%)	22 (12.6%)
Death/MI	9 (13.2%)	11 (7.1%)	13 (7.5%)
Death	1 (1.5%)	1 (0.6%)	0 (0.0%)
MI	8 (11.8%)	11 (7.1%)	13 (7.5%)

a. In this table only endpoints that occurred from the time of PTCA until day 30 of the study are included.

### 7.0.3.2c Analysis of the subjects by receipt of PTCA in the PRISM trial

The sponsors also performed a post-hoc analysis of the subsequent clinical events that occurred to subjects in the PRISM trial who had a PTCA, in part mirroring the population studied in the RESTORE trial. The PRISM analyses include all subjects with a PTCA, either during the initial or following a readmission. It was not possible to identify the PTCA procedure as occurring during the initial hospitalization or following a readmission due to the design of the case report forms and the collection of this information in the database. The subjects who had PTCA represents a minority population of the entire PRISM trial: 320/1616 (19.8%) in the tirofiban group; 334/1616 (20.7%) in the heparin group.

**7.0.3.2c Analysis of the subjects by receipt of PTCA in the PRISM trial (cont)**

The table below summarizes the clinical events for subjects during the first 30 days, according to whether they received PTCA or not. This same analysis is shown for the PRISM-PLUS above. The shaded boxes highlight the post-PTCA subgroup. In all subgroups, the incidence of the composite endpoint and its components was lower in the tirofiban group, compared with heparin. Note that for the subjects who did not undergo PTCA, the event rates were quite low, and there was no difference between the tirofiban and heparin group event rates for the composite endpoint or for MI.

Table 7.0.3.2c.1 (from table 6.2.1.12.3.5) Clinical events in during the first 30 days grouped according to receipt of PTCA in the PRISM trial<sup>a</sup>.

Procedure	Tirofiban n=320/1616 (19.8%)	Heparin n=334/1616 (20.7%)
<b>Composite Endpoint (RIC, MI, Death)</b>		
All subjects	257/1616 (15.9%)	276/1616 (17.1%)
Subjects who underwent PTCA	71/320 (22.2%)	94/334 (28.1%)
Prior to PTCA only	50/320 (15.6%)	73/334 (21.9%)
Subsequent to PTCA only <sup>b</sup>	21/320 (6.4%)	35/334 (10.5%)
Subjects who did not undergo PTCA	186/1296 (14.4%)	182/1282 (14.2%)
<b>MI (fatal/ nonfatal)</b>		
All subjects	66/1616 (4.1%)	69/1616 (4.3%)
Subjects who underwent PTCA	22/320 (6.9%)	25/334 (7.5%)
Prior to PTCA only	14/320 (4.4%)	15/334 (4.5%)
Subsequent to PTCA only	8/320 (2.5%)	10/334 (3.0%)
Subjects who did not undergo PTCA	44/1296 (3.4%)	44/1282 (3.4%)
<b>Death</b>		
All subjects	37/1616 (2.3%)	59/1616 (3.6%)
Subjects who underwent PTCA	1/320 (0.3%)	7/334 (2.1%)
Prior to PTCA only	0/320 (0.0%)	0/334 (0.0%)
Subsequent to PTCA only	1/320 (0.3%)	7/334 (2.1%)
Subjects who did not undergo PTCA	36/1296 (2.8%)	52/1282 (4.1%)

a. Data from NDA 20-912, volume 1.42, reference 5, table 27, adjoining text, and from personal communication with sponsor.

b. Counts the clinical events from the time of PTCA out to the end of 30 days.

The table above summarizes clinical events that occurred during the first 30 days of after start of the study. This means that an individual who had PTCA on day 23 (for example) would have follow-up information for only an additional 7 days. The FDA performed a similar analysis looking at events that occurred during the first 7 days after PTCA, where a larger % of the subjects have data for all 7 days. This is presented only for those subjects who received PTCA, since they are the only group affected by the 30 day cut-off for follow-up (those who did not get PTCA have clinical event data for an entire 30 days).

Table 7.0.3.2c.2 (from table 6.2.1.12.3.6) Clinical events in during the first 7 days following receipt of PTCA in the PRISM trial<sup>a</sup>.

Procedure	Tirofiban n=320/1616 (19.8% of total)	Heparin n=334/1616 (20.7% of total)
<b>Composite Endpoint (RIC, MI, Death)</b>	12 (3.8%)	13 (3.9%)
<b>MI (fatal/ nonfatal)</b>	7 (2.2%)	9 (2.7%)
<b>Death</b>	1 (0.3%)	4 (1.2%)

a. Data from electronic datasets and SAS analysis per FDA.

As discussed above, the number of subjects in the PRISM trial who received PTCA while on study drug was too small (10 total) to allow for meaningful analysis of clinical event rates.

7.0.3.2d Analysis of the subjects by receipt of PTCA in the RESTORE trial

Analysis of the post-PTCA subjects in the RESTORE trial

This section is placed here for purposes of comparison with the results above for the PRISM-PLUS and PRISM trials. In the RESTORE trial, all subjects received study drug in conjunction with PTCA, and the incidence of clinical endpoints is shown below.

Table 7.0.3.2d.1 (from table 6.2.3.12.2d.1) Incidence of the combined endpoint and its components at 48 hours, 7, 30, and 180 days<sup>a</sup> in the RESTORE trial. The primary endpoint is shaded.

	Tirofiban <sup>a</sup> n=1071	Placebo <sup>c</sup> n=1070	95% Confidence Intervals	p value <sup>b</sup>
<b>Combined endpoint at 48 hours<sup>d</sup></b>	58 (5.4%)	93 (8.7%)	0.425, 0.840	0.003
<b>Combined endpoint at 7 days</b>	<b>81 (7.6%)</b>	111 (10.4%)	0.522, 0.951	0.022
<b>Combined endpoint at 30 days (primary endpoint)</b>	<b>110 (10.3%)</b>	130 (12.2%)	<b>0.632, 1.084</b>	<b>0.169</b>
<b>Combined endpoint at 180 days (secondary endpoint)</b>	258 (24.1%)	290 (27.1%)	0.702, 1.037	0.110
<b>CABG at 48 hours</b>	<b>10 (0.9%)</b>	15 (1.4%)	0.291, 1.461	0.299
<b>CABG at 7 days</b>	13 (1.2%)	17 (1.6%)	0.402, 1.139	0.436
<b>CABG at 30 days</b>	20 (1.9%)	23 (2.2%)	0.469, 1.575	0.623
<b>CABG at 180 days</b>	59 (5.5%)	73 (6.8%)	0.556, 1.130	0.199
<b>Repeat PTCA at 48 hours</b>	12 (1.1%)	34 (2.2%)	0.176, 0.666	0.002
<b>Repeat PTCA at 7 days</b>	29 (2.7%)	47 (4.4%)	0.377, 0.967	0.036
<b>Repeat PTCA at 30 days</b>	45 (4.2%)	58 (5.4%)	0.514, 1.142	0.191
<b>Repeat PTCA at 180 days</b>	168 (15.7%)	183 (17.1%)	0.717, 1.135	0.378
<b>Stent placement at 48 hours<sup>e</sup></b>	16 (1.5%)	27 (2.5%)	0.314, 1.096	0.094
<b>Stent placement at 7 days</b>	16 (1.5%)	27 (2.5%)	0.314, 1.095	0.094
<b>Stent placement at 30 days</b>	16 (1.5%)	27 (2.5%)	0.314, 1.096	0.094
<b>Stent placement at 180 days</b>	16 (1.5%)	27 (2.5%)	0.314, 1.095	0.094
<b>MI (both fatal and non-fatal) at 48 hours</b>	29 (2.7%)	47 (4.4%)	0.373, 0.960	0.033
<b>MI (both fatal and non-fatal) at 7 days</b>	39 (3.6%)	57 (5.3%)	0.438, 1.010	0.055
<b>MI (both fatal and non-fatal) at 30 days</b>	45 (4.2%)	61 (5.7%)	0.485, 1.069	0.104
<b>MI (both fatal and non-fatal) at 180 days</b>	67 (6.3%)	81 (7.6%)	0.578, 1.132	0.216
<b>Death at 48 hours</b>	2 (0.2%)	2 (0.2%)	0.136, 6.953	0.979
<b>Death at 7 days</b>	4 (0.4%)	4 (0.4%)	0.246, 3.964	0.986
<b>Death at 30 days</b>	9 (0.8%)	8 (0.7%)	0.433, 2.930	0.808
<b>Death at 180 days</b>	19 (1.8%)	15 (1.4%)	0.644, 2.521	0.487

a. Data from NDA 20-912, volume 1.55, table 8-22. Intent-to-treat population is used, confirmed by FDA analysis.

b. p value per the sponsor based on logistic regression analysis.

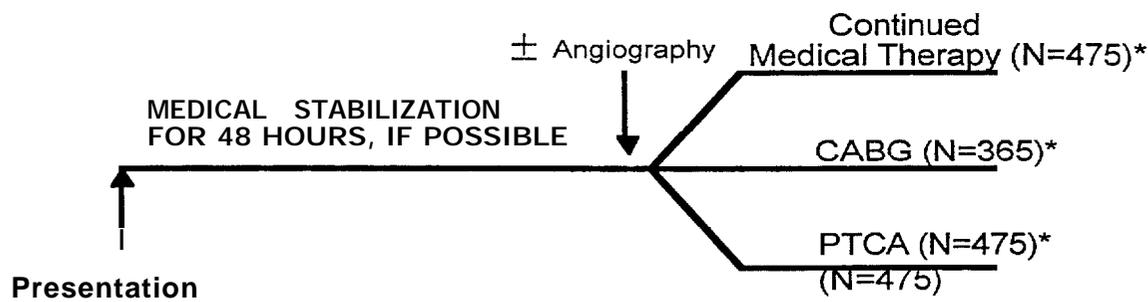
c. Both groups also received heparin bolus during the PTCA/atherectomy as well as ASA, unless individually contraindicated.

d. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a stent because of procedural failure.

e. Stent placement refers to those stents placed after the initial PTCA for procedure failure.

### 7.0.3.3 Analysis of the subjects by receipt of PTCA or CABG in the PRISM-PLUS trial

The sponsor also sought to define the clinical benefit of tirofiban in the presence or absence of major invasive cardiac procedures by analyzing the PRISM-PLUS trial according to the receipt of CABG or PTCA. Because the tirofiban alone arm was discontinued from the trial, only the tirofiban +heparin and heparin-alone groups were analyzed. In the PRISM-PLUS, subjects were to undergo 48 hours of medical stabilization prior to angiography. This angiography, presumably, provided guidance to the investigators with regard to further cardiac interventions. Subjects were then followed for the use of further cardiac interventions through 30 days. Three groups were formed: those who had either PTCA or CABG during their hospitalization and those who had not interventional procedure (see figure below from sponsor).



**Figure 1. Patient Triage During the index Hospitalization in the PRISM PLUS Trial**

• N = Number of Patient Who Received Tirofiban + Heparin or Heparin Alone

As a caveat, the sponsor points out that there was a nominally significant effect of tirofiban on clinical outcomes by the end of 48 hours (the 'stabilization period'). As a result, subjects randomized to tirofiban +heparin or heparin alone may have had different levels of risk related to interventional strategies.

Next, the sponsor summarized the occurrence of clinical events in the three populations for up to 30 and up to 180 days. Based on these data, the sponsor argues that there was a treatment benefit for tirofiban +heparin, when compared with heparin alone in all three sub-groups. Note that the largest differences between treatment groups are in the PTCA group, with the least difference seen in the group which did not receive either intervention ('medical management').

### 7.0.3.3 Analysis of the subjects by receipt of PTCA or CABG in the PRISM-PLUS trial (cont)

Figure 7.0.3.3.1 Incidence of clinical events up to 30 days in the PTCA, CABG and 'medical management' groups from the PRISM-PLUS trial<sup>c</sup>.

Procedure	Tirofiban +Heparin	Heparin	Odds Ratio	95% Confidence Intervals
<b>Composite Endpoint (RIC, MI, Death)</b>				
All Patients	143/773 (18.5%)	178/797 (22.3%)	0.769	0.599-0.987
Patients who underwent PTCA	43/239 (18.0%)	57/236 (24.2%)	0.672	0.427-1.056
Prior to PTCA only	24/239 (10.0%)	30/236 (12.7%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to PTCA only	21/239 (8.8%)	36/236 (15.2%)	0.528	0.297-0.940
Patients who underwent CABG	52/181 (28.7%)	61/184 (32.3%)	0.803	0.513-1.260
Prior to CABG only	48/181 (26.5%)	59/184 (32.1%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to CABG only	15/181 (8.3%)	18/184 (9.8%)	0.820	0.398-1.691
Patients who underwent Med Mgmt	51/344 (14.8%)	63/375 (16.8%)	0.843	0.560-1.269
<b>Death/MI</b>				
All Patients	67/773 (8.7%)	95/797 (11.9%)	0.695	0.499-0.967
Patients who underwent PTCA	21/239 (8.8%)	31/236 (13.1%)	0.648	0.359-1.168
Prior to PTCA only <sup>b</sup>	7/239 (2.9%)	10/236 (4.2%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to PTCA only	14/239 (5.9%)	24/236 (10.2%)	0.558	0.280-1.110
Patients who underwent CABG	22/181 (12.2%)	31/184 (16.8%)	0.679	0.376-1.227
Prior to CABG only <sup>b</sup>	17/181 (9.4%)	28/184 (15.2%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to CABG only	15/181 (8.3%)	17/184 (9.2%)	0.871	0.419-1.813
Patients who underwent Med Mgmt	27/344 (7.8%)	38/375 (10.1%)	0.746	0.444-1.254

a. NA = Not Applicable. Odds ratios with respect to event prior to the procedures not calculated because the time window during which events were counted (randomization to start of procedure) is directly related to the effect of the treatments and could vary systematically between treatment groups.

b. All events were myocardial infarctions.

c. Data from sponsor, and has not been verified by FDA analysis.

The sponsor also examined the incidence of clinical events for up to 180 days in the same three populations.

Figure 7.0.3.3.2 Incidence of clinical events up to 180 days in the PTCA, CABG and 'medical management' groups from the PRISM-PLUS trial<sup>c</sup>.

Procedure	Tirofiban +Heparin	Heparin	Risk Ratio	95% Confidence Intervals
<b>Composite Endpoint (RIC, MI, Death)</b>				
All Patients	214/773 (27.7%)	256/797 (32.1%)	0.811	0.677-0.973
Patients who underwent PTCA	76/239 (31.8%)	90/236 (38.1%)	0.753	0.555-1.024
Prior to PTCA only	24/239 (10.0%)	30/236 (12.7%)	NA	NA
Subsequent to PTCA only	59/239 (24.7%)	73/236 (30.9%)	0.734	0.521-1.035
Patients who underwent CABG	59/181 (32.6%)	70/184 (38.0%)	0.793	0.560-1.123
Prior to CABG only	48/181 (26.5%)	59/184 (32.1%)	NA	NA
Subsequent to CABG only	24/181 (13.3%)	33/184 (17.9%)	0.711	0.420-1.204
Patients who underwent Med Mgmt	81/344 (23.6%)	99/375 (26.4%)	0.869	0.648-1.166
<b>Death/MI</b>				
All Patients	95/773 (12.3%)	122/797 (15.3%)	0.775	0.593-1.014
Patients who underwent PTCA	24/239 (10.0%)	34/236 (14.4%)	0.676	0.400-1.141
Prior to PTCA only <sup>b</sup>	7/239 (2.9%)	10/236 (4.2%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to PTCA only	18/239 (7.5%)	27/236 (11.4%)	0.634	0.349-1.153
Patients who underwent CABG	28/181 (15.5%)	39/184 (21.2%)	0.692	0.426-1.125
Prior to CABG only	17/181 (9.4%)	28/184 (15.2%)	NA <sup>a</sup>	NA <sup>a</sup>
Subsequent to CABG only	22/181 (12.2%)	26/184 (14.1%)	0.837	0.474-1.477
Patients who underwent Med Mgmt	46/344 (13.4%)	54/375 (14.4%)	0.905	0.611-1.342

a. NA = Not Applicable. Odds ratios with respect to event prior to the procedures not calculated because the time window during which events were counted (randomization to start of procedure) is directly related to the effect of the treatments and could vary systematically between treatment groups.

b. All events were myocardial infarctions.

c. Data from sponsor, and has not been verified by FDA analysis.

7.0.3.4 Effect of Tirofiban on the Number of Cardiac Procedures

In the phase III trials, the sponsor collected data on the frequency of cardiac procedures in each of the treatment arms. One possible clinical benefit for tirofiban would be to reduce the need for such procedures. In the three phase III trials, no such benefit was detected for any cardiac procedure.

In the PRISM-PLUS trial, no trend towards fewer procedures was detected in the tirofiban +heparin group when compared with the heparin-alone group.

Table 7.0.3.4.1 (from table 6.2.1.12.3.10) Cardiac procedures during first 30 days of PRISM-PLUS<sup>a</sup>.

Procedure	Tirofiban n=334	Tirofiban +Heparin n=773	Heparin n=797	p value (T+H vs H) <sup>b</sup>
<b>Any cardiac procedure</b>	319 (92.5%)	708 (91.6%)	719 (90.2%)	0.38
Angiography	316 (91.6%)	704 (91.1%)	710 (89.1%)	0.21
<b>Any revascularization</b>	205 (59.4%)	444 (57.4%)	442 (55.5%)	0.44
Angioplasty	109 (31.6%)	242 (31.3%)	239 (30.0%)	0.58
Atherectomy	3 (0.9%)	5 (0.6%)	8 (1.0%)	0.58
Stent	23 (6.7%)	70 (9.1%)	50 (6.3%)	0.046
CABG	88 (25.5%)	194 (25.1%)	200 (25.1%)	0.99
<b>IABP</b>	20 (5.8%)	36 (4.7%)	40 (5.0%)	0.81
<b># of procedures per subject (mean ±SD)</b>	1.76±1.01	1.74±1.01	1.69±1.04	0.20

a. Data from NDA 20-912, volume 1.42, reference 5, table 23.

b. p value per the sponsor based on logistic regression analysis, comparing heparin (H) versus the combination (T +H).

Similarly, in the PRISM trial, no trend towards fewer procedures was detected in the tirofiban +heparin group when compared with the heparin-alone group.

Table 7.0.3.4.2 (from table 6.2.2.12.3.4) Cardiac procedures during first 30 days of PRISM<sup>a</sup>.

Procedure	Tirofiban n=1616	Heparin n=1616	p value <sup>b</sup>
<b>Any cardiac procedure</b>	1072 (66.3%)	1062 (65.7%)	0.74
Angiography	998 (61.8%)	1005 (62.2%)	0.83
<b>Any revascularization</b>	624 (38.6%)	609 (37.7%)	0.61
Angioplasty	320 (19.8%)	334 (20.7%)	0.57
Atherectomy	11 (0.7%)	10 (0.6%)	0.99
Stent	123 (7.6%)	99 (6.1%)	0.11
CABG	296 (18.3%)	269 (16.6%)	0.23
<b>IABP</b>	43 (2.7%)	31 (1.9%)	0.20
<b># of procedures per subject (mean ±SD)</b>	1.16±1.10	1.14±1.10	0.60

a. Data from NDA 20-912, volume 1.48, table 24.

b. p value per the sponsor based on logistic regression analysis.

Finally, in the RESTORE trial, no evidence of a difference between the two groups was detected.

Table 7.0.3.4.3 (from table 6.2.3.12.3.3) Cardiac procedures performed after initial PTCA/atherectomy RESTORE<sup>a</sup>.

	Tirofiban (n=1071)	Placebo (n=1070)	p value
<b>Any cardiac procedures</b>	435 (40.6%)	442 (41.3%)	0.745
<b>IABP</b>	18 (1.7%)	26 (2.4%)	0.228
<b>Other cardiac procedure</b>	291 (27.2%)	269 (25.1%)	0.302

a. Data from NDA volume 1.55, ref. 11, table 25 and electronic datasets. Shown as n(%).

b. p value calculated using chi square analysis.

## 8.0 to 8.2 Integrated Safety Summary for Tirofiban

The safety review is broken into three logical sections:

8.0 Methodologies used for Safety Review

8.1 Background Database for Safety Review

8.2 Summary of Safety Review

### 8.0 Methodologies Used for Safety Review

#### 8.0.1 Subsections of the Integrated Safety Review and Preliminary Comments

Section 8.0 will use the following outline:

1) Source materials for the safety review, including the numbers of subjects exposed in each of the treatment groups, along the extent of exposure;

2) General methodologies used to elicit adverse events within the database;

3) **Specific** search strategies used in the **tirofiban** database. This will include a discussion of the sponsor's decision to split the subjects receiving **heparin** into two groups for purposes of safety event comparison.

#### 8.0.2 Source Materials and Methods for the Integrated Safety Review

The **tirofiban** NDA database includes 12 human trials, as summarized below. Details of the data submitted for each of these trials is to be found in sections 1.1 and 5.1 above, as well as in the reviews of each study. All of the data included in this section was received by Merck on or before the final data cutoff date of 2.24.97 for the phase II studies and 4.10.97 for the phase III studies. No long-term follow-up safety data is available to this reviewer.

Table 8.0.2.1 Overview of Tirofiban clinical development program.

Protocol	Study Population	# of Subjects	Study Drug(s)	Control Group
<b>Clinical Pharmacology Studies</b>				
#001	Healthy Subjects	44	Tirofiban	Placebo
#002	Healthy Subjects	12	Tirofiban ± ASA	Placebo
#004	Stable CAD <sup>b,c</sup>	24	Tirofiban ± ASA	Placebo Subjects with CAD
#009	Hepatic Insufficiency	24	Tirofiban	Placebo Healthy Subjects
#012	Healthy Subjects	6	<sup>14</sup> C-Tirofiban	None
#014	Renal Insufficiency	31	Tirofiban	Placebo (Healthy Subjects)
<b>Phase II Dose-Ranging Studies<sup>c</sup></b>				
#005	UAP/NQWMI <sup>c</sup>	102	Tirofiban	Heparin
#007	ACS for PTCA <sup>d</sup>	93	Tirofiban +Heparin	Placebo
#008	UAP/NQWMI	48	Tirofiban +Heparin	Heparin
<b>Phase III Clinical Efficacy &amp; Safety Studies<sup>e</sup></b>				
#006 (PRISM-PLUS)	UAP/NQ WMI	1915	Tirofiban +Heparin Tirofiban	Heparin
#011 (PRISM)	UAP/NQWMI	3232	Tirofiban	Heparin
#013 (RESTORE)	ACS for PTCA	2141	Tirofiban +Heparin	Heparin

a. Data from NDA volume 1.2.

b. CAD: coronary artery disease.

c. UAP/NQWMI: unstable angina pectoris/ non-Q-wave MI.

d. ACS for PTCA: acute coronary syndrome for percutaneous transluminal angioplasty.

e. In all trials enrolling subjects with coronary artery disease, the subjects also received ASA 325 mg/day unless contraindicated for the individual subject.

Of these twelve studies, the database for the **tirofiban** safety review is drawn from the 6 phase II-III studies listed below. The safety review for the remaining 6 phase I-II studies was conducted as part of each individual review, performed by Dr. Pellayo. Any pertinent findings from his safety review will be integrated into the discussion of individual adverse events in the relevant sections below.

## 8.0.2 Source Materials and Methods for the Integrated Safety Review (cont)

The next two tables summarize the phase II-III population, first by the type of subjects and total number in each trial, and then by study drug administration.

Table 8.0.2.2 Studies using tirofiban incorporated into the safety database<sup>a</sup>.

Protocol	Study Population	Number of Subjects	Study Drug(s)	Control Group
<b>Phase II Dose-Ranging Studies<sup>c</sup></b>				
#005	UAP/NQWMI <sup>c</sup>	102	Tirofiban	Heparin
#007	ACS for PTCA <sup>d</sup>	93	Tirofiban +Heparin	Placebo
#008	UAP/NQWMI	48	Tirofiban +Heparin	Heparin
<b>Phase III Clinical Efficacy &amp; Safety Studies<sup>c</sup></b>				
#006 (PRISM-PLUS)	UAP/NQWMI	1915	Tirofiban +Heparin	Heparin
#011 (PRISM)	UAP/NQWMI	3232	Tirofiban	Heparin
#013 (RESTORE)	ACS for PTCA <sup>d</sup>	2141	Tirofiban +Heparin	Heparin

a. Data from NDA volume 1.2.

b. CAD: coronary artery disease.

c. UAP/NQWMI: unstable angina pectoris/ non-Q-wave MI.

d. ACS for PTCA: subjects with acute coronary syndrome who receive percutaneous transluminal angioplasty.

e. In all trials enrolling subjects with coronary artery disease, the subjects also received ASA 325 mg/day unless contraindicated for the individual subject.

Table 8.0.2.3 Number of subjects in the Phase II-XII trials, grouped according the study drug(s) administered<sup>a</sup>.

Protocol	# of Tirofiban Subjects	# of Tirofiban + Heparin Subjects	# of Heparin Subjects
<b>Phase II Dose-Ranging Studies</b>			
#005	71		31
#008		36	12
#007		73	20
<b>Phase III Clinical Efficacy &amp; Safety Studies</b>			
#006 (PRISM-PLUS)	345	773	797
#011 (PRISM)	1616		1616
#013 (RESTORE)		1071	1070
<b>Total</b>	2032	1953	3546
<b>Corrected Total<sup>b</sup></b>	2002	1946	3546

a. Data from NDA volumes 1.42, 1.48, 1.55.

b. Subtracting 30 subjects who were randomized to receive Tirofiban, and 7 who were randomized to receive Tirofiban +Heparin, but failed to receive study drug (NDA volume 1.2, Table C-34).

### Collection of safety data

The safety data collected for each of these six trials, and the time during which the data was collected, are summarized in the tables below. In the three largest trial, AEs were collected for 24 hours after the end of the tirofiban infusion, and SAEs for 30 days following the end of the tirofiban infusion. Across all the Phase II/III studies, non-serious adverse experiences were reportable from the time of randomization through 24 hours after cessation of the infusion of study drugs. Serious adverse experiences in the Phase III studies were reportable from the time of randomization through Day 30 after start of study drug in the PRISM and PRISM-PLUS studies; in RESTORE, adverse events were reportable up to 30 days after the completion of the study drug infusion.

In PRISM and PRISM-PLUS, recurrent angina during the initial hospitalization period was documented on the case report form but was not reported as an adverse event since it was the condition for which the patient was being treated. It should also be noted that in the Phase III studies, certain protocol-specified adverse experiences that were also clinical endpoints of the trial were not captured on the adverse experience case report form, however, and were only reported as endpoints. For example, refractory ischemia and new myocardial infarction during initial hospitalization were only reported as endpoints.

Finally, the collection of deaths and hospitalizations after 30 days needs to be commented on. Follow-up for the 180 day timepoint could be done by phone. Additionally, no 180 day follow-up was performed for the PRISM trial. This will be important for determining the mortality rate after 180 days.

## 8.0.2 Source Materials and Methods for the Integrated Safety Review (cont)

### Collection of data on bleeding complications

In the Phase II/III trials, all bleeding complications were considered adverse experiences and reported both on the bleeding complication case report form and the adverse event case report form. The severity of the bleeding on the case report form was categorized as oozing, mild, moderate, severe, or life-threatening. A bleeding adverse event was to be classified as either a clinical adverse experience (e.g., groin hematoma) or a laboratory adverse experience (e.g., urine blood present). If a patient was discontinued from the study due to a bleeding event, the patient was classified as a discontinuation due to a bleeding AE (whether clinical or laboratory). Therefore, the counts tables of discontinuations due to bleeding complications include clinical bleeding events and laboratory bleeding events resulting in study drug cessation.

Table 8.0.2.4 Safety data collected in the trials for mine the safety database<sup>a</sup>.

Study	Deaths	AU Adverse Events	Selected Adverse Events <sup>b</sup>	Case Report Forms <sup>d</sup>	Time of Follow-up for AEs
#005	Y	Y	Y	Y	Through 24 hours of infusion for all AEs
#007	Y	Y	Y	N	Through 24 hours of infusion and 10 hours post-infusion for all AEs
#008	Y	Y	Y	N	Through 48 hours of infusion for all AEs
#006 (PRISM-PLUS)	Y	Y		Y	Through 24 hours post-infusion for all AEs
#011 (PRISM)	Y	Y	Y	Y	30 days for SAEs Through 24 hours post-infusion for all AEs
#013 (RESTORE)	Y	Y	Y <sup>c</sup>	Y	30 days for SAEs Through 24 hours post-infusion for all AEs 30 days for SAEs

a. Data from NDA volumes 1.55, 1.42, 1.59, and 1.48, and from electronic datasets.

b. Certain adverse events were pre-specified to have special attention paid to their occurrence. Examples include bleeding adverse events and thrombocytopenia.

c. The RESTORE trial protocol specified certain events which would not be included as adverse, as they pertained to potential endpoints or are expected results of PTCA. For details see the RESTORE trial review.

d. CRFs were submitted electronically.

Table 8.0.2.5 Timing of laboratory data collection in the trials for mine the NDA 20-912 safety database<sup>a</sup>.

Study	Complete Lab Values <sup>c</sup>	Hematology <sup>b</sup>	PT/aPTT	Physical Exam
#005	0, 24, & 48 hrs	0, 0.5, 2, 6, 12, 24, 36, 48, & 60 hrs	0, 6, 24, 48, & 60 hrs	0, 24, & 48 hrs
#007	0, 2, 6, & 24 hours <sup>d</sup>	0, 2, 6, & 24 hours <sup>d</sup>	0, 6, 12, & 24 hours <sup>d,e</sup>	0, and 16-24 hrs
#008	0, 24, & 48 hrs	0, 0.5, 2, 6, 12, 24, 36, 48, & 60 hrs	0, 6, 24, 48, & 60 hours	0, 24, & 48 hrs
#006 (PRISM-PLUS)	0, 24, 48, 72, 96, & 120 hours	6 hours	0, 6, 12, 24, 48, 72, & 96 hrs	0, 24, 48, 72, 96 & 120 hours
#011 (PRISM)	0, 24, 48, & 72 hrs	6 hours	0, 6, 12, 24, & 48 hrs	0, 24, 48, & 72 hrs
#013 (RESTORE)	0 & 36 hours	6 and 24 hours	0 & 36 hrs	0 & 36 hours

a. Data from NDA volumes 1.55, 1.42, 1.59, and 1.48, and from electronic datasets.

b. Hematology includes hemoglobin & hematocrit. This was also included in the complete lab evaluations.

c. A complete lab evaluation included: CBC with differential; serum chemistries; urinalysis; and stool for occult blood (where available).

d. Depending on the subject, another PT/aPTT could be drawn between 16 and 24 hours.

e. Measurements were also made 10 hours after end of infusion.

### 8.0.3 Extent of Subject Exposure to Study Drug

These subjects in the six trials that form the safety database are shown below, arranged according to the study drug administered.

Table 8.0.3.1 Number of subjects in the Phase II-III trials, grouped according the study drug(s) administered<sup>a</sup>.

Protocol	# of Tirofiban Subjects	# of Tirofiban + Heparin Subjects	# of Heparin Subjects
<b>Phase II Dose-Ranging Studies</b>			
#005	71		31
#008		36	12
#007		73	20
<b>Phase III Clinical Efficacy &amp; Safety Studies</b>			
#006 (PRISM-PLUS)	345	773	797
#011 (PRISM)	1616		1616
#013 (RESTORE)		1071	1070
<b>Total</b>	<b>2032</b>	<b>1953</b>	<b>3546</b>
<b>Corrected Total<sup>b</sup></b>	<b>2002</b>	<b>1946</b>	<b>3546</b>

a. Data from NDA volumes

b. Subtracting 30 subjects who were randomized to receive Tirofiban, and 7 who were randomized to receive Tirofiban +Heparin, but failed to receive study drug (NDA volume 1.2, Table C-34).

The dose and duration of exposure to tirofiban was discussed in section 5.1.1 above. This included a discussion of the variability in the amount and duration of tirofiban infusion in each of the three phase III trials. Two of the summary tables from that section are included below, showing the numbers of subjects exposed to a given dose and time of tirofiban administration. Overall, greater than 95% of the subjects received tirofiban or placebo for less than 100 hours.

Table 8.0.3.2 Cumulative tirofiban dose exposure for the subjects in the Phase II-III trials<sup>a</sup>.

Cumulative Dose (mgs)	Tirofiban (n=2002)	Placebo (n=1946)	Combined (n=3948)
>0 to <5	18	125	143
≥5 to <10	32	67	99
210 to 45	46	80	126
115 to <20	59	81	140
≥20 to <25	142	377	519
≥25 to <30	268	426	694
≥30 to <35	530	310	840
≥35 to <40	365	200	565
≥40 to <45	236	132	368
≥45 to <50	101	83	184
≤50 to 555	63	31	94
≥55 to <60	45	19	64
≥60 to <65	39	11	50
≥65 to <70	27	2	29
≥70 to <75	10	1	11
≥75 to <80	9	0	9
≥80 to <85	6	0	6
285 to 190	5	0	5
≥90 to <95	1	0	1
≥95 to <100	0	0	0
≥100 to ≤105	0	0	0
≥105 to ≤110	0	1	1

Data from NDA volume 1.2, table C-4, for those randomized subjects who received at least one dose of study drug.

### 8.0.3 Extent of Subject Exposure to Study Drug (cont)

Table 8.0.3.3 Cumulative time of tirofiban exposure for the subjects in the Phase II-III trials.

Duration of Exposure (hours)	Tirofiban (n=2002)	Placebo (n=1946)	Combined (n=3948)
>0 to <5	14	109	123
≥5 to <10	25	30	55
≥10 to <15	19	25	44
≥15 to <20	22	59	81
≥20 to <25	36	51	87
≥25 to <30	10	20	30
≥30 to <35	12	35	47
≥35 to <40	8	863	871
≥40 to <45	29	15	44
≥45 to <50	1506	85	1591
≥50 to ≤55	38	42	80
≥55 to <60	8	18	26
≥60 to <65	27	52	79
≥65 to <70	25	75	100
≥70 to <75	96	185	281
≥75 to <80	16	21	37
≥80 to <85	14	30	44
≥85 to <90	11	48	59
≥90 to <95	28	61	89
≥95 to <100	51	104	155
≥100 to <105	0	5	5
≥105 to <110	6	10	16
≥110 to <115	0	3	3
≥115 to <120	0	0	0

### 8.0.4 General Methodologies Used for Safety Review

This section details the examination of AEs in the tirofiban safety database. In general, this was accomplished by examination of data from the six Phase II-III trials, comparing the incidence of a given AE in the control group with the group receiving tirofiban. Wherever possible, all AEs potentially linked to the administration of tirofiban are further examined for dose-, time-, sex-, age-, race-dependency. These examinations will be complicated by the different regimens employed in each of the trials for both the dose and duration of tirofiban administration (see sections 5.1.3 and appendix 8, section 20.0). Due to time constraints, the majority of the datasets examined have been prepared by the sponsor, and no independent confirmation of their accuracy has been performed. Any primary analysis performed by FDA reviewers will be identified as such.

The time-dependency of an AE will be examined both in terms of the time of onset of a given AE, as well as the duration or severity of a given AE. When examining the association of drug administration to a given AE, increased significance will be given to AEs which occur during or shortly after study drug administration. For example, a bleeding AE which occurs 10 days after the end of tirofiban administration is less likely to be related to drug administration than one that occurs within hours of starting tirofiban.

The relationship between a given AE and a demographic population (i.e., females, subjects with hepatic insufficiency) will be explored by comparing the incidence rate of a given AE in the target population with that in the combined database.

#### 8.0.4.1 Approach to Eliciting Deaths and Serious Adverse Events

In the tirofiban NDA, an adverse experience (AE) was considered serious if the event resulted in one of the following: death; permanent or substantial disability; inpatient hospitalization; prolongation of existing inpatient hospitalization; cancer; or congenital anomaly. An adverse experience was also considered serious if it was considered to be immediately life-threatening, or was identified as such by the individual investigator. Overdoses (accidental or intentional) were also considered to be serious adverse experiences, whether or not they resulted in any clinical sequelae.

Each of the Phase III trials was performed under the auspices of an independent DSMB. As specified in the respective protocols, the DSMBs had access to interim, unblinded safety reports throughout the conduct of the trials. The DSMBs reviewed the safety data at regular intervals, and when deemed necessary, recommended appropriate modifications to the protocol or the program in general. To allow for proper blinding and adjudication of critical efficacy endpoints that also met the definition of serious adverse experiences, the Merck was granted a waiver by the FDA for reporting of these prospectively defined endpoints to regulatory agencies. Therefore, with the exception of death (which was always reported as both a clinical endpoint and a serious adverse event), potential clinical endpoints in the respective Phase III trials that occurred during the initial hospitalization period were not reported as serious adverse events, only endpoints. After discharge from the initial hospitalization through the 30-day follow-up period, all clinical endpoints meeting the definition of a serious adverse event were reported both as serious adverse experiences and as endpoints. The clinical endpoints or potential endpoints covered by this waiver, and the reporting guidelines for the respective protocols, are illustrated in the table below.

Table 8.1.2.1 Guidelines for reporting of clinical endpoints qualifying as serious adverse events in the Phase III trials of NDA 20-912<sup>a</sup>.

Clinical Endpoints	Events Occurring During the Initial Hospitalization	Events Occurring During 30-Day Follow-up	Events Occurring During 6-Month Follow-up <sup>b</sup>
<b>Unstable Angina Trials (PRISM-PLUS and PRISM)</b>			
Refractory ischemia	Endpoint only	Not applicable	Not applicable
New myocardial infarction	Endpoint only	Endpoint + SAE	Endpoint only
Death	Endpoint + SAE	Endpoint + SAE	Endpoint only
Readmission for unstable angina	Not applicable	Endpoint + SAE	Endpoint only
<b>Coronary Angioplasty (PTCA) Trial (RESTORE)</b>			
Repeat revascularization	Endpoint only	Endpoint + SAE	Endpoint only
Stent placement for procedure failure	Endpoint only	Endpoint + SAE	Endpoint only
New myocardial infarction	Endpoint only	Endpoint + SAE	Endpoint only
Death Endpoint only	Endpoint + SAE	Endpoint + SAE	Endpoint only

a. Data from NDA volume 1.37, Table D-28 and individual study summaries,

b. Refers only to the PRISM-PLUS and RESTORE trials.

#### 8.0.4.2 Approach to Eliciting Adverse Events

Adverse experiences were defined as any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body or worsening of a preexisting condition temporally associated with the use of the study drug (active drug, control agents or placebo), whether or not they were considered to be related to the use of the product. Clinical adverse experiences determined by the investigator or volunteered by the patient were recorded throughout the study reporting period. Results from laboratory tests and any special examinations (i.e., physical examinations including vital signs, electrocardiograms, etc.) also were reviewed by the investigator to determine if any of the findings were adverse experiences.

When an adverse experience occurred, the investigator recorded pertinent information about the event on the case report form, including: date and time of onset; whether the event was a serious adverse experience; the relationship of the adverse experience to the study drug; the action taken regarding the test drug (i.e., none or drug discontinued); or whether the adverse experience caused the patient to be discontinued from the study. Additionally, for clinical adverse experiences, the investigator recorded the maximum intensity of the event, the date the adverse experience stopped, and its duration. Maximum intensity was recorded using a three-point scale of intensity: mild (easily tolerated); moderate (interfering with usual activity); or severe (incapacitating). The relationship between the adverse experience and the test drug was graded by the investigator using a five-point scale as follows: definitely not, probably not, possibly related, probably related, or definitely related.

#### 8.0.4.2 Approach to Eliciting Adverse Events (cont)

It should also be noted that in the Phase III studies, certain protocol-specified adverse experiences that were also clinical endpoints of the trial were not captured on the adverse experience case report form, however, and were only reported as endpoints. For example, refractory ischemia and new myocardial infarction during initial hospitalization were only reported as endpoints. Therefore, with the exception of death (which was always reported as both a clinical endpoint and a serious adverse event), potential clinical endpoints in the respective Phase III trials that occurred during the initial hospitalization period were not reported as serious adverse events, only endpoints. After discharge from the initial hospitalization through the 30-day follow-up period, all clinical endpoints meeting the definition of a serious adverse event were reported both as serious adverse experiences and as endpoints.

The critical tables from the sponsor that were used to identify adverse events were:

1. NDA volume 1.2, Table C-37 (Nonbleeding clinical adverse events);
2. NDA volume 1.2, Table C-39 (Bleeding clinical adverse events).

#### 8.0.4.3 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

The terms used by the individual investigators to describe individual adverse events were mapped to COSTART terminology by the sponsor. No sponsor's dictionary, detailing what terms were collected under each COSTART term is available. Instead, this reviewer submitted a list of COSTART terms to the sponsor, who then provided a listing of the individual event descriptions mapped to it. These will be discussed as appropriate in section 8.2

#### 8.0.4.4 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Key adverse event, in this usage, means an adverse event which will be discussed because it may be linked to the use of tirofiban. First, any adverse event identified in the tirofiban safety database occurring in >1% of the subjects in any group will be tabulated, and the percentage compared. Those AEs which occur with a differential frequency between two and control groups will be examined, and if there is a consistent pattern, discussed further. The group of bleeding AEs is an example of AEs identified using such an approach.

Any adverse event linked to the administration of other members of the GP IIb/IIIa platelet receptor antagonists will also be discussed (see sections 2.2.2). Thrombocytopenia and neutropenia are two AEs which are discussed further because of their links to other GP IIb/IIIa platelet receptor antagonists.

Finally, certain safety AEs are routinely investigated as part of any NDA submission. An example of such an AE, discussed further in section 8.1.7.4, is abnormal liver function tests (LFTs).

#### 8.0.4.5 Laboratory Adverse Event Incidence

Laboratory safety measurements (hematology, serum chemistry, urinalysis, and miscellaneous) were performed at regular intervals during the clinical trials reported in this submission (see table 8.0.2.1). Since not all patients had all laboratory tests performed, the denominator for a laboratory adverse experience varies, and is the number of patients who had that laboratory test performed. The reporting of any laboratory adverse experience was always dependent on the individual investigator's assessment of its clinical importance. Thus, laboratory values within or outside the normal range could be interpreted as adverse by one investigator and not by another.

### 8.0.4.5.1 Extent of Laboratory Testing in the Development Program

Table 8.1.6.1.1 below summarizes the collection of laboratory data in the Phase II-III database. Of the three large phase III trials, PRISM and PRISM-PLUS collected lab data at least three time points following the start of study drug administration. In contrast, RESTORE trial collected only two sets of labs: one at baseline and one set 36 hours later. As a result, the incidence of detected lab abnormalities can be expected to be higher in the PRISM and PRISM-PLUS trials.

Table 8.1.6.1.1 Timing of laboratory data collection in the trials forming the NDA 20-912 safety database<sup>a</sup>.

Study	Complete Lab Values <sup>c</sup>	Hematology <sup>b</sup>	PT/ aPTT
#005	0,24, & 48 hrs	0, 0.5, 2, 6, 12, 24, 36, 48, & 60 hrs	0, 0.5, 2, 6, 12, 24, 36, 48, & 60 hrs
#007	0, 2, 6, & 24 hours	0, 2, 6, & 24 hours	0, 6, 12, & 24 hours
#008	0,24, &60 hrs	0,0.5, 2, 6, 12, 24, 36, 48, & 60 hrs	0, 6, 24, 48, & 60 hours
#006 (PRISM-PLUS)	0, 24, 48, 72, 96, & 120 hours	6 hours	0, 6, 12, 24, 48, 72, & 96 hrs
#011 (PRISM)	0, 24, 48, & 72 hrs	6 hours	0, 6, 12, 24, & 48hrs
#013 (RESTORE)	0 & 36 hours	6 hours	0 & 36 hrs

a. Data from NDA volumes 1.55, 1.42, 1.49, and 1.48, and from electronic datasets.

b. Hematology includes hemoglobin & hematocrit. This was also included in the complete lab evaluations.

c. A complete lab evaluation included: CBC with differential; serum chemistries (electrolytes, BUN, **creatinine**, ALT/AST, albumin, calcium, CPK, glucose, magnesium, phosphate, bilirubin); urinalysis (for protein, glucose, blood, bilirubin); and stool for occult blood (where available).

#### Follow-up for abnormal laboratory findings

In Phase II and Phase III, investigators were instructed to provide outcome for all adverse experiences, and it was expected that abnormal laboratory values would be followed through resolution. No specific follow-up criteria were outlined, however, for abnormal laboratory values.

#### Laboratory testing

In the Phase II program (Protocols 005, 007, 008), all protocol-required laboratory tests were performed locally at the individual study sites. This was also the case for the Phase III study, RESTORE (Protocol 013). In the Phase III unstable angina trials, PRISM-PLUS and PRISM (Protocols 006 and 011), all protocol-required serum chemistries were sent to a central laboratory. Hematology, urinalysis, cardiac enzymes, and stool exams were performed locally at the individual study sites. Coagulation parameters (prothrombin time and partial thromboplastin time) were also performed locally, however the results were kept blinded to the investigator staff caring for the patients. Only the 'unblinded' investigator(s) at the site was aware of the results of the coagulation parameters.

Plasma **tirofiban** levels in protocols 005, 007, and 008 were batched, and analyzed at a central Merck lab.

For Protocol 005, the frozen samples arrived in a total of 21 shipments between May 26, 1993, and January 11, 1994.

For Protocol 007, the frozen samples arrived in a total of 26 shipments between November 2, 1993 and July 22, 1994.

For Protocol 008, the frozen samples arrived in a total of 9 shipments between December 15, 1993 and November 3, 1994.

Plasma samples from all three studies were continually analyzed in a rollout fashion. No study batches were done due to the inconsistent timing of the shipments and workloads resources at Merck Research Laboratories. However, study results were not provided to the sponsor's Clinical Research section until the individual study had been officially unblinded. After unblinding of the study, a Biopharmaceutics Report was prepared and incorporated into the clinical study report.

#### 8.0.4.6 Specific Search Strategies Unique to the Tirofiban Review

The majority of the estimates of incidence of specific AEs will be based on the pooled data from the six phase II-III studies. This is based on the homogeneity of the patient population entered into the trials. Specific explorations which will also be carried out include the following:

##### 1. Explorations for Drug Disease Interactions

###### a. Renal and hepatic disease

The subjects in protocol 009 (hepatic insufficiency) and 014 (renal insufficiency) will also be examined separately, due to their comorbid disease processes which may increase their potential for bleeding. This will include an examination of any altered pharmacokinetics of tirofiban in these populations.

Subjects in the phase III trials with either renal or hepatic insufficiency will be searched for in the electronic datasets and their AEs compared with those of the larger phase III population.

###### b. Cardiovascular disease

The AEs that occurred to subjects with hypertension prior to entry into one of the three phase III trials will be collected and compared with the entire population.

###### c. Diabetes and hypercholesterolemia

The AEs that occurred to subjects with either diabetes or hypercholesterolemia prior to entry into any of the phase III trials will be collected and compared with the entire population.

##### 2. Drug-Class specific AEs

The safety profiles of the other IIb/IIIa receptor antagonists (see section 2.2.2) also dictate that specific attention be paid to the incidence of bleeding, thrombocytopenia, neutropenia/ agranulocytosis, and the development of platelet antibodies. No information regarding platelet antibodies was submitted in this NDA.

##### 3. Duration of Exposure-related AEs

An attempt will be made to examine the incidence of bleeding and any other AEs associated with tirofiban administration in terms of the duration of exposure to study drug. This examination will be limited by the different doses and durations of therapy used in the three pivotal trials (see section 5.1.3, p. 22, and appendix 10, page 370 for discussion).

##### 4. Explorations for Drug-drug interactions

The AEs occurring to subjects taking the following medications will be compared with the AEs of the larger phase III population: thrombolytics (ticlid, warfarin, low-molecular weight heparin); cardiovascular drugs (calcium channel blockers, nitrates, & blockers); and non-steroidal anti-inflammatory drugs (NSAIDs).

#### 8.0.4.7 Methodological issues related to group comparisons of AEs

The sponsor argues that the subjects who received heparin should be split into two groups: one group who also underwent procedures; and one group of subjects who were not scheduled to undergo procedures by protocol. The stated reason, per discussion with the sponsor, was to devise a comparator group for the subjects who received only tirofiban (without heparin), especially for adverse events related to bleeding. All but 36 patients (from Protocol 008) of the 1953 patients in the tirofiban-plus-heparin group were in trials that involved study drug therapy administered during invasive cardiac procedures. For instance, in the PRISM-PLUS trial, subjects were expected to undergo angiography after 48 hours, while still receiving study drug. In the RESTORE trial, tirofiban and heparin were administered during angioplasty. The sponsor argues that this population is different from the subjects in the PRISM trial, which did not explicitly call for intervention at a specified time point. Per the sponsor, the majority of the interventions that occurred in the PRISM trial occurred after discontinuation of the study drug infusion. A comparison of the percentage of subjects who received invasive cardiac procedures is shown below. Note that while fewer subjects in the PRISM trial had cardiac procedures than the subjects in PRISM-PLUS, a substantial fraction of them still received either angiography or angioplasty within the first 30 days (the cut-off for SAE reporting). More subjects in the PRISM-PLUS trial underwent CABG in the *first* 30 days. Note also that the subjects in the PRISM-PLUS trial had far fewer angioplasties or atherectomies than the group in the RESTORE trial.

Table 8.0.4.7.1 Incidence of specific cardiac procedures within first 30 days of the PRISM, PRISM-PLUS, and RESTORE trials<sup>a</sup>.

Study	Angiography	Angioplasty	Atherectomy	CABG	Stent placement
PRISM <sup>b</sup> (tirofiban, n=3232)	2003 (62%)	6.54 (20.2%)	21 (0.64%)	565 (17.5%)	222 (6.9%)
PRISM-PLUS <sup>c</sup> (tirofiban, n=1915)	1730 (90.3%)	590 (30.1%)	16 (0.80%)	482 (25.2%)	143 (7.5%)
RESTORE <sup>d</sup> (tirofiban, n=2140)	2140 (100%)	1980 (93%)	159 (7.4%)	46 (2.2%)	175 (8.2%)

a. Data from individual study summaries and electronic datasets, NDA-20-912, and from sponsor.

b. PRISM data is shown for first 30 day after start of study drug (see NDA 20-718, volume 2.47, section 6.2.2).

c. PRISM-PLUS data is shown for first 30 day after start of study drug (see NDA 20-912, volume 1.42, section 3, table 23).

d. RESTORE data is shown for the initial procedure for PTCA, angiography and atherectomy, since all subjects underwent angiography ± PTCA/atherectomy (see NDA 20-912, volume 1.55, table 11). CABG data is shown for first 30 days.

The sponsor argues that the adverse experience profile of patients undergoing procedures is different than the profile of patients in whom procedures are not performed. For example, bleeding risks (from the femoral artery puncture site) are different; nausea and vomiting (from dye reactions) can be increased; back and pelvic pain (from measures taken to maintain groin hemostasis) can be expected to occur more frequently in patients undergoing procedures. The same considerations apply to the heparin control groups. Because of the difference in rates of adverse experiences associated with procedures, the sponsor separated the heparin-treated patients in the Phase II/III trials into two groups for the purpose of the safety analysis.

The first group included patients from the trials in which invasive procedures were performed during study drug administration (n=1887), from the RESTORE, PRISM-PLUS, and the Phase II angioplasty trial (Protocol 007), which the sponsor argues is the appropriate comparator group for tirofiban plus heparin. It should be noted that the subjects in the PRISM and RESTORE trial differ from each other in some important aspects, particularly with regards to the dose of heparin administered. In the PRISM-PLUS trial, the average heparin dose was approximately 76,500 U (see table 6.2.1.12.2c.3 in the PRISM-PLUS trial summary). In contrast, the average dose of heparin in the RESTORE trial was only 11,000 U (see table 6.2.3.12.2c.3 in the RESTORE trial summary).

The second group included only patients from trials in which procedures were proscribed during study drug administration (n=1659); from PRISM, and the two Phase II UAP/NQWMI studies (protocols 005, OOS), which the sponsor argues is a good comparator group for tirofiban alone.

For the purposes of section 8.1, the primary analysis will be the usual safety analysis: the incidence of AEs and SAEs in the database will be compared between three groups (tirofiban alone, tirofiban +heparin, heparin alone). Where appropriate, a separate analysis comparing the tirofiban alone group with heparin-treated 'without procedures' and comparing the tirofiban +heparin group with the heparin-treated 'with procedure' group will be included.

## 8.1 Background Database for Safety Review

In the integrated safety summary, adverse events will be examined in the following order:

- 1) Deaths;
  - 2) Serious Adverse Events (SAEs);
  - 3) Adverse Events (AEs) related to clinical findings;
  - 4) Adverse Events related to laboratory findings and special examinations;
- and
- 5) Subject discontinuations.

Following this, selected adverse events will be examined, using the phase II-III database:

- 1) Special studies, including tolerance, overdose, withdrawal/ rebound, abuse potential, and human reproduction;
  - 2) Selected adverse events either linked to the administration of tirofiban or other IIb/IIIa inhibitors;
- and
- 3) Selected adverse events examined during normal examination of safety as part of all NDA reviews, including subgroup analyses of adverse events according to gender, race, age, and common clinical characteristics.

### 8.1.1 Deaths in the tirofiban safety database

Deaths will be examined first in the overall database, and then in each trial. During the review of the PRISM-PLUS trial, the decision to withdraw the tirofiban-alone arm will be examined.

#### 8.1.1.1 Integrated data on deaths in the PRISM, PRISM-PLUS, and RESTORE trials

##### Overall crude mortality rate at the end of 30 days

The first two tables summarize the mortality rate at the end of 30 days. The first table summarizes the rate of death only for those subjects who died on or prior to day 30.

Table 8.1 .1. 1.1 Crude 30 day mortality rate from the combined Phase II-III studies for NDA 20-912”.

Treatment group	Deaths/Pt.# (30 days)	Crude Mortality (30 days)
Tirofiban	58/ 2032	2.85%
Tirofiban + Heparin	37/ 1953	1.89%
Heparin	103/ 3546	2.90%

- a. Data from individual study volumes and individual study summaries. Analysis based on ITT population.
- b. Rate calculated using 30 **day** follow-up **date from** the PRISM trial, as well as 180 day follow-up data from the PRISM-PLUS and RESTORE trials. Since no data is available, this analysis assumes there were no deaths in the PRISM trial after 30 days (unlikely).
- c. Rate calculated only from the 180 day follow-up data **from** the PRISM-PLUS and RESTORE trials. For this calculation, the total population is as follows: tirofiban 416; tirofiban +heparin 1953; and **heparin 1930 subjects**.

The second table, from the sponsor, includes subjects whose deaths occurred outside the 30 day follow-up period for whom case report material was available. **These** included 3 tirofiban, 6 heparin, and 2 combination subjects. Note that in the table below, the subjects who received heparin are divided into 'Heparin/ Procedure and Heparin/ No Procedure. This division was discussed in section 8.0.4.7.

Table 8.1.1.1.2 Crude 30-day mortality rate from the combined Phase II-III studies for NDA 20-912”.

Treatment group	Deaths/IV. # (30 days)	Crude Mortality (30 days)
<b>Tirofiban Alone</b>	61/2032	3.0%
<b>Heparin / No Procedure</b>	62/1659	3.7%
<b>Tirofiban + Heparin</b>	39/1953	2.0%
<b>Heparin / Procedure</b>	47/1887	2.5%
<b>Total Heparin Alone</b>	109/3546	3.1%

a. Data from NDA volume 1.37, Table D-44.

##### Overall crude mortality rate at the end of 180 days

Because differences in the duration of follow-up, the table below summarizes the incidence of death at 180 days in two ways, depending on the population chose for detection. The sponsor did not prepare a summary of the 180 day mortality.

8.1.1.1 Integrated data on deaths in the PRISM, PRISM-PLUS, and RESTORE trials (cont)

Table 8.1.1.1.3 Crude 180 day mortality rate from the combined Phase II-III studies for NDA 20-912”.

Treatment group	Deaths/ Total Population (%) (180 days) <sup>b</sup>	Deaths/ Total Population (%) (180 days) <sup>c</sup>
Tirofiban	62/ 2032 (3.05%)	25/ 416 (6.00%)
Tirofiban + Heparin	72/ 1953 (3.69%)	72/ 1953 (3.69%)
Heparin	130/ 3546 (3.67%)	71/ 1930 (3.68%)

- a. Data from individual study volumes and individual study summaries. Analysis based on ITT population
- b. Rate calculated using 30 day follow-up date from the PRISM trial, as well as 180 day follow-up data from the PRISM-PLUS and RESTORE trials. Since no data is available, this analysis assumes there were no deaths in the PRISM trial after 30 days (unlikely).
- c. Rate calculated only from the 180 day follow-up data from the PRISM-PLUS and RESTORE trials. For this calculation, the total population is as follows: tirofiban 416; tirofiban +heparin 1953; and heparin 1930 subjects.

Causes of death in the phase II-III tirofiban database

The first table summarizes the reported cause of death for all 204 subjects in the safety database with available death narratives and CRFs. The subjects were grouped according to whether the death was due to cardiac causes (i.e., ventricular tachycardia, recurrent MI), or non-cardiac causes (i.e., sepsis), and are expressed as a % of the total, deaths in each group. A majority of the deaths in all trials were due to cardiac events.

Table 8.1.1.1.4 Causes of death from the PRISM-PLUS, PRISM, and RESTORE trials”.

Treatment Group	Total Number of Deaths	Cardiac	Non-cardiac	Unknown <sup>b</sup>
Tirofiban (n=2032)	61	43 (61%)	16 (26%)	2 (3%)
Tirofiban +Heparin (n=1953)	37	31 (84%)	4 (11%)	2 (5%)
Heparin (n=3546)	106	76 (72%)	27 (25%)	3 (3%)
<b>Total</b>	<b>204</b>	<b>150 (74%)</b>	<b>47 (23%)</b>	<b>7 (3%)</b>

- a. Data comes from inspection of individual patient death summaries (see section 14.0) and CRFs by medical reviewer.
- b. Any subject who died suddenly at home and no notation of arrhythmia or other cardiac information was classified as unknown.

The next table summarizes the number of deaths in each treatment group associated with either a significant bleeding event or a cerebrovascular accident (CVA). Bleeding was considered significant if it contributed to the death of the subject, based on a review of the narratives and CRFs. Note that the tirofiban +heparin group had a higher incidence of death associated with bleeding, when expressed as a % of deaths in each category, including bleeding which occurred while on study drug. A lower % of deaths in the tirofiban +heparin arm were associated with CVAs.

Table 8.1.1.1.5 Deaths associated with bleeding or CVAs from PRISM-PLUS, PRISM, and RESTORE<sup>a</sup>.

Treatment Group	Total Number of Deaths	Associated with Bleeding	Associated Temporally with Bleeding <sup>b</sup>	Associated with a CVA
Tirofiban (n=2032)	61	5 (8%)	3 (4.9%)	5 (8%)
Tirofiban +Heparin (n=1953)	37	9 (24%)	4 (10.8%)	1 (3%)
Heparin (n=3546)	106	16 (14%)	5 (4.8%)	10 (9%)
<b>Total</b>	<b>204</b>	<b>30 (15%)</b>	<b>12 (5.9%)</b>	<b>17 (8%)</b>

- a. Data comes from inspection of individual patient death summaries (see appendix 2, section 14.0) and CRFs by medical reviewer.
- b. Column counts only those subjects that developed bleeding during administration of study drug. Data obtained in consultation with sponsor.

**8.1.1.1 Integrated data on deaths in the PRISM, PRISM-PLUS, and RESTORE trials (cont)**

The deaths in the table below were associated with clinically significant bleeding. Details of each case will be discussed below. The subjects with adverse events described in bold letters developed bleeding while still receiving study drug.

Table 8.1 .I. 1.6 List of deaths associated with bleeding adverse events from the PRISM-PLUS, PRISM, and RESTORE trials<sup>a</sup>.

Subject #	Bleeding adverse event
<b>Tirofiban</b>	
006-044 AN 6250	GI hemorrhage, mesenteric ischemia
006-050 AN 6547	'Major bleeding' 4 days after D/C of study drug
011-023 AN 2518	DIC 7 days after D/C of study drug
011-114 AN 5597	Cardiac tamponade
011-155 AN 6552	Melena
<b>Tirofiban +Heparin</b>	
006-095 AN 1567	Cardiac tamponade 7 days after D/C of study drug
006-049 AN 6591	'Excessive blood loss' >4 days after D/C of study drug
006-048 AN 7243	Groin site bleeding requiring transfusion 2 days after D/C of study drug
006-092 AN 7483	<b>Hemoperitoneum</b>
006-102 AN 5604	Thoracic aortic dissection, starting 1 day after study drug D/C
013-003 AN 1286	<b>Intracranial hemorrhage</b>
013-021 AN 1777	<b>Retroperitoneal hemorrhage</b>
013-021 AN 1809	<b>Retroperitoneal hemorrhage &amp; cardiac tamponade</b>
013-003 AN 3144	GI hemorrhage starting after D/C of study drug
<b>Heparin</b>	
006-034 AN 1067	Heme-arthrosis 20 days after study drug D/C
006-084 AN 1234	<b>Retroperitoneal hemorrhage</b>
006-057 AN 5310	<b>Groin hematoma, pulmonary embolism</b>
006-059 AN 6155	'Uncontrolled bleeding' starting 9 days after study drug D/C
006-043 AN 6676	Retroperitoneal hemorrhage developing 14 days after study drug D/C
006-034 AN 6981	Pulmonary hemorrhage after Swann-Ganz misplacement 21 days after D/C of study drug
006-094 AN 7613	Coronary artery dissection after stent placement 3 days after D/C of study drug
01 I-092 AN 1320	Intracranial hemorrhage 9 days after D/C of study drug
01 I-092 AN 2467	Mediastinal bleeding 11 days after D/C of study drug
011-065 AN 3280	Hemorrhagic CVA 14 days after D/C of study drug
011-061 AN 5160	<b>Groin hematoma requiring transfusion</b>
01 I-072 AN 7001	DIC 6 days after D/C of study drug, following a CABG
013-045 AN 1425	GI hemorrhage following sepsis, 6 days after D/C of study drug
013-030 AN 1445	<b>Retroperitoneal hemorrhage</b>
013-020 AN 2932	<b>Groin hematoma</b>

a. Data comes from inspection of individual patient death summaries (see section 14.0) and CRFs by medical reviewer.

### 8.1.1.1 Integrated data on deaths in the PRISM, PRISM-PLUS, and RESTORE trials (cont)

The following deaths were associated with new CVAs. Those CVAs which were identified in the database as hemorrhagic are noted.

Table 8.1 .1.1.7 List of deaths associated with new CVAs from the PRISM-PLUS, PRISM, and RESTORE trial?

Subject #	Hemorrhagic CVA?
<b>Tirofiban</b>	
006-057 AN 6623	
011-021 AN 1724	
011-061 AN 3620	
<b>011-123</b> AN 3888	
011-167 AN 7859	
<b>Tirofiban +Heparin</b>	
<b>013-003</b> AN 1286	Hemorrhagic
<b>Heparin</b>	
006-037 AN 1303	
006-043 AN 6676	Hemorrhagic
011-092 AN 1320	Hemorrhagic
01 I-085 AN 2809	
011-061 AN 3091	
01 I-065 AN 3280	
011-060 AN 4041	
011-127 AN 4902	
011-061 AN 4972	
<b>013-053</b> AN 1954	

a. Data comes from inspection of individual patient death summaries (see section 8.0) and CRFs by medical reviewer.

### 8.1.1.2 Deaths from individual studies

For all of the trials, the duration of follow-up after the end of the study drug infusion varied. See table 8.0.2.4 and 8.0.2.5 for details of the follow-up for each trial.

Death summaries were provided for subjects up to 30 days after study drug administration, and are included in appendix 2 below. Details of these summaries were compared with individual case report forms (CRFs) where possible. A total of 209 narratives are included in appendix two from the PRISM-PLUS, PRISM, and RESTORE trials. For another 61 subjects from the PRISM-PLUS and RESTORE trials, who are known to have died between 30 and 180 days after study drug administration, no details of the cause of death, and no death narratives, are available.

#### Sources of data for individual deaths

1. Individual study reviews (NDA volume 1.40, 1.42, 1.46, 1.47, 1.48 and 1.55) for summary statistics and individual subject narratives (up to 30 day follow-up).
2. Appendices 4.1.1 from Reference #006 and # 011 from electronic datasets for 180 day follow-up data for individual subjects.
3. NDA volume 1.37, Safety Summary for summary statistics.

#### 8.1.1.2a Deaths from protocol #005

There were no deaths reported during the trial period for protocol #005 (A Randomized, Double-Blind, Heparin-Controlled, Dose-Finding Study of MK-0383 in Subjects With Unstable Angina Pectoris).

#### 8.1.1.2b Deaths from protocol #007

There were no deaths reported during the trial period for protocol #007 (A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of MK-0383 in High-Risk Subjects Undergoing Percutaneous Transluminal Coronary Angioplasty).

#### 8.1.1.2c Deaths from protocol #008

There were no deaths reported during the trial period for protocol #008 (A Randomized, Double-Blind Study of MK-0383 in Subjects With Unstable Angina Pectoris Concomitantly Receiving Heparin).

8.1.1.2d Deaths from PRISM-PLUS (protocol #006)

The data for the incidence of death in the PRISM-PLUS trial are summarized in the table below, representing the final tallies for all reported subjects. Through 30 days of follow-up, 85 subject deaths had been reported. At the end of the 180 day follow-up, there were 134 reported deaths.

Table 8.1.1.2d.1 Deaths in the PRISM-PLUS trial"

Time of Follow-up	Tirofiban alone n=345	Tirofiban + Heparin n=773	Heparin alone n=797	Total n=1915
48 hours	2 (0.6%)	1 (0.1%)	2 (0.2%)	5 (0.3%)
7 days	16 (4.6%)	15 (1.9%)	15 (1.9%)	46 (2.4%)
30 days	21 (6.1%)	28 (3.6%)	36 (4.5%)	85 (4.4%)
180 days	25 (7.2%)	53 (6.9%)	56 (7.0%)	134 (7.0%)

a. Data from NDA volume 1.42, tables 17-20.

Subject death narratives from PRISM-PLUS are included in appendix two (section 14.0).

Note the smaller number of subjects enrolled in the tirofiban alone arm. This arm was discontinued after 345 subjects were randomized (of 420 proposed) due to concerns over the apparent excess mortality rate at the end of 48 hours and 7 days, as discussed in the next section.

Withdrawal of tirofiban-alone arm from the PRISM-PLUS trial

The trial was designed to be under the guidance of an unblinded Data Safety Monitoring Board (DSMB) which was to conduct two protocol-specified interim analyses of safety and efficacy after one-third and two-thirds of the originally projected sample size were enrolled in the study. The first interim analysis was performed as planned, but at the time of this analysis, the DSMB elected to not unblind any efficacy data because there were too few endpoint events and none had been adjudicated. Instead the DSMB recommended reevaluating efficacy after 50% of the originally projected sample size had been enrolled. This second interim analysis took place after 30-day efficacy results were available for just over 200 subjects per group. At the time of this analysis, the DSMB recommended that the trial discontinue enrollment in one of the tirofiban treatment arms (it turned out to be the tirofiban-alone arm) due to an excess mortality at the 7-day endpoint. The DSMB also recommended an increase in the sample size of the trial to 735 subjects per group for the remaining two arms.

The data shown to the DSMB at the time of the second interim analysis on November 13, 1995, are summarized below. The incidence of deaths in each of the groups is highlighted. First, the event rates in the tirofiban group are compared with the heparin group. Then, the tirofiban +heparin group is compared with heparin. The excess mortality was seen at day 7 (4.8% tirofiban vs. 1.4% heparin, p=0.056). Note that the total number of subjects in each category was a fraction of the total ultimately in each group: tirofiban 210/345 (60.5%); tirofiban +heparin 213/773 (27.6%); and heparin 211/797 (26.4%).

Table 8.1.1.2d.2 Incidence of the primary endpoint (RI/MI/Death) and its components at 48 hours, 7, 30, and 180 days in the PRISM-PLUS trial".

	Tirofiban n=210	Tirofiban +Heparin n=213	Heparin n=211	p value (T vs H) <sup>b</sup>	p value (T+H vs H) <sup>b</sup>
Combined endpoint at 48 hours	16 (7.6%)	21 (9.9%)	17 (8.1%)	0.84	0.57
Combined endpoint at 7 days	38 (18.1%)	31 (14.5%)	32 (15.2%)	0.42	0.87
Combined endpoint at 30 days	50 (23.8%)	42 (19.7%)	38 (18.0%)	0.15	0.67
RIC at 48 hours	16 (7.6%)	20 (9.4%)	16 (7.6%)	0.99	0.55
RIC at 7 days	35 (16.7%)	29 (13.6%)	31 (14.7%)	0.57	0.76
RIC at 30 days	46 (21.9%)	36 (16.9%)	37 (17.5%)	0.26	0.86
MI (both fatal and non-fatal) at 48 hours	2 (1.0%)	3 (1.4%)	6 (2.8%)	0.19	0.35
MI (both fatal and non-fatal) at 7 days	12 (5.7%)	5 (2.4%)	13 (6.2%)	0.89	0.063
MI (both fatal and non-fatal) at 30 days	16 (7.6%)	10 (4.7%)	18 (8.5%)	0.74	0.12
Death at 48 hours	3 (1.4%)	1 (0.5%)	1 (0.5%)	NA	NA
Death at 7 days	10 (4.8%)	3 (1.4%)	3 (1.4%)	0.056	0.98
Death at 30 days	11 (5.2%)	4 (1.9%)	4 (1.9%)	0.068	0.98
MI/Death at 48 hours	4 (1.9%)	4 (1.9%)	6 (2.8%)	0.55	0.54
MI/Death at 7 days	19 (9.0%)	8 (3.8%)	13 (6.2%)	0.24	0.28
MI/Death at 30 days	24 (11.4%)	14 (6.6%)	18 (8.5%)	0.31	0.46

a. Data from NDA 20-912, volume 1.42, tables 17-20 and volume 1.59, reference 55, table 1. Intent-to-treat population is used.

b. p value per the sponsor based on logistic regression analysis, comparing tirofiban (T), tirofiban +heparin (T +H) with heparin (H).

c. RIC: refractory ischemic conditions, including: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on ECG despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention within 12 hours of symptom onset.

### 8.1.1.2d Deaths from PRISM-PLUS (protocol #006) (cont)

The DSMB was to use its best judgment in determining whether to discontinue a trial for safety. Because there were subjects who had enrolled in the PRISM-PLUS trial whose data were not available at the time of the look summarized above, the DSMB requested an up-to-date tabulation of deaths at the end of 7 days, as reported to the sponsor. These data, presented to the DSMB on November 15, 1995, are shown in the table below. A listing of the subject deaths that were available to the DSMB at this time is found in appendix 12, section 24.0.

Table 6.2.1.12.3.5 Incidence of the death at 7 days in the PRISM-PLUS trial as of 11.15.95<sup>a</sup>.

	Tirofiban n=314	Tirofiban +Heparin n=314	Heparin n=314	p value (T vs H) <sup>b</sup>	p value (T+H vs H) <sup>b</sup>
Death at 7 days	14 (4.5%)	5 (1.6%)	4 (1.3%)	0.029	1.00

a. Data from NDA 20-912, volume 1.59, tables 2 and appendix 4.1.2.

b. p value per the sponsor based on logistic regression analysis, comparing tirofiban (T) or tirofiban +heparin (T +H) with heparin

(H).

Per the sponsor, these findings 'confirmed the concern for excess mortality in the tirofiban-alone arm'. The DSMB was particularly concerned about this arm, because the use of heparin represented the 'standard of care' for subjects with unstable angina (tirofiban alone was considered 'experimental therapy'). The DSMB felt it was inappropriate to withhold heparin, especially in light of the positive results they were already seeing in the combination arm. Based on these considerations, and the persistent, nominally significant excess mortality in the tirofiban arm, the DSMB recommended the discontinuation of the tirofiban alone group on November 17, 1995. After discussions with the Steering Committee, all enrolling sites were then notified and no further subjects enrolled in the tirofiban arm as of December 8, 1995. The identity of the arm was kept confidential from all investigators at the request of the Steering Committee until the unblinding of the study.

After completion of the trial, with all data collected and adjudicated, the sponsor summarized results of the trial for the cohort of subjects enrolled prior to December 8, 1995, and those results are shown below.

Table 6.2.1.12.3.6 Final incidence of the primary endpoint (RI/MI/Death) and its components at 48 hours, 7, and 30 days in the 12.8.95 cohort'.

	Tirofiban n=345	Tirofiban +Heparin n=336	Heparin n=350
Combined endpoint at 48 hours	26 (7.5%)	19 (5.6%)	24 (6.9%)
Combined endpoint at 7 days	59 (17.1%)	39 (11.6%)	59 (16.9%)
Combined endpoint at 30 days	81 (23.5)	63 (18.8%)	78 (22.3%)
RIC at 48 hours	23 (6.7%)	17 (5.1%)	20 (5.7%)
RIC at 7 days	39 (11.3%)	29 (8.6%)	45 (12.9%)
RIC at 30 days	44 (12.8%)	35 (10.4%)	48 (13.7%)
MI (both fatal and non-fatal) at 48 hours	5 (1.4%)	2 (0.6%)	6 (1.7%)
MI (both fatal and non-fatal) at 7 days	24 (7.0%)	9 (2.7%)	25 (7.1%)
MI (both fatal and non-fatal) at 30 days	31 (9.0%)	19 (5.6%)	32 (9.1%)
Death at 48 hours	2 (0.6%)	0 (0%)	1 (0.3%)
Death at 7 days	16 (4.6%) <sup>d</sup>	5 (1.5%)	4 (1.1%)
Death at 30 days	21 (6.1%) <sup>e</sup>	7 (2.1%)	14 (4.0%)

a. Data from NDA 20-912, volume 1.59, tables 3, reference 57.

b. p value per the sponsor based on logistic regression analysis, comparing tirofiban(T) or tirofiban +heparin (T +H) with heparin

(H).

c. RIC: refractory ischemic conditions, including: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention within 12 hours of symptom onset.

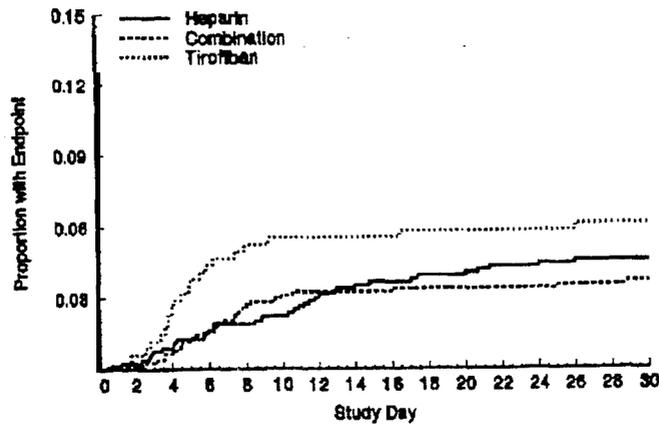
d. p value for tirofiban vs. heparin 0.21 per sponsor's analysis. p value =0.011 using Fisher's Exact Test.

e. p value = 0.228 using Fischer's Exact Test.

### 8.1.1.2d Deaths from PRISM-PLUS (protocol #006) (cont)

The time course of the effect of tirofiban +heparin, tirofiban alone, and heparin alone on the incidence of death for up to 30 days is shown in the figure below for all subjects in the NDA database.

Figure 8.1.1.2d Incidence of death during the PRISM-PLUS trial.



The increased incidence of deaths in the tirofiban alone group persisted when the three groups were followed out to 180 days, although the significance of the difference was lost (see table 8.1.1.1d.1 above). As is discussed below, there did not seem to be an excess of death associated with either cardiovascular AEs, bleeding AEs, or CVAs in the tirofiban group (see table 8.1.1.2.2). Note also that the subjects in the PRISM trial, who were randomly administered either tirofiban or heparin, showed no differential incidence of death up to 30 days (see table 8.1.1.2e. 1 below). In that trial the incidence of death was non-significantly lower in the tirofiban group at the end of 7 days, when compared with subjects receiving heparin (the comparator group in the PRISM trial). The sponsor is not seeking an indication for the administration of tirofiban without co-administration of heparin.

### 8.1.1.2e Deaths from PRISM (protocol #011)

Through 30 days of follow-up, 96 subject deaths were reported for the PRISM trial. Per protocol, no 180 day follow-up data were collected. Compared with heparin, there was no indication that tirofiban alone was associated with an increased mortality. In fact, there was a nominally significant reduction in mortality in the tirofiban group at the end of 30 days, relative to heparin.

Table 8.1.1.2e. 1 Deaths in the PRISM trial<sup>a</sup>.

Time of Follow-up	Tirofiban n=1616	Heparin n=1616	p-value <sup>b</sup>
48 hours	6 (0.4%)	4 (0.2%)	0.54
7 days	16 (1.0%)	25 (1.6%)	0.15
30 days	37 (2.3%)	59 (3.6%)	0.021

a. Data from NDA volume 1.48, reference 9, tables 20-27.  
b. p value per the sponsor for tirofiban versus heparin.

Subject death narratives from PRISM are included in appendix two (section 14.0).

### 8.1.1.2f Deaths from RESTORE (protocol #013)

Through 30 days of follow-up, 96 subject deaths were reported for the RESTORE trial. At the end of 180 days of follow-up, there were 34 reported deaths. The narratives for individual deaths in the RESTORE trial appear in appendix 2.

Table 8.1.1.2f. 1 Deaths in the RESTORE trial<sup>a</sup>.

Time of Follow-up	Tirofiban +Heparin n=1071	Heparin n=1070	Total n=2141	p-value <sup>b</sup>
48 hours	2 (0.2%)	2 (0.2%)	4 (0.2%)	0.979
7 days	4 (0.4%)	4 (0.4%)	8 (0.4%)	0.986
30 days	9 (0.8%)	8 (0.7%)	17 (0.8%)	0.808
180 days	19 (1.8%)	15 (1.4%)	34 (1.6%)	0.487

a. Data from NDA volume 1.55, reference 11, table 22.  
b. p value per the sponsor.

### 8.1.2 Other Serious Adverse Events (SAEs) in the Phase II-III Safety Database

The table below shows the number and percentage of subjects had reported SAEs reported by the individual investigators ( $\geq 0.5\%$ ) in any treatment group by body system, or SAEs with particular interest for this compound (i.e., bleeding SAEs) which occurred at a lower rate. The serious adverse events noted during each trial are summarized to be found in the individual trial reviews. Note that the number of deaths includes a small number of subjects who died after the 30 day follow-up period (compare with table 8.1.1.2.1). Shaded numbers reflect those SAEs where the incidence of a given SAE in the heparin group was  $>2$  times or  $<0.5$  times the rate in either the tirofiban alone or tirofiban +heparin groups. A listing of all reported SAEs in the database is found in appendix 15, organized by the study drug administered to each subject.

Table 8.1.2.1 Serious adverse events collected in the phase II-III safety database<sup>a</sup>.

Body System/ SAE	Tirofiban + Heparin n=1953	Heparin Procedures n=1887	Tirofiban n=2032	Heparin No Procedures n=1659	Total Heparin Alone n=3546
<b>Total # with SAEs</b>	386 (20%)	352 (18.7%)	375 (18%)	296 (17.8%)	648 (18%)
<b>Total # without SAEs</b>	1567 (80%)	1535 (81.3%)	1657 (82%)	1363 (82.2%)	2898 (82%)
<b>Body as a whole</b>	154 (7.9%)	153 (8.1%)	129 (6.3%)	<b>125 (7.5%)</b>	278 (7.8%)
Death	39 (2.0%)	47 (2.5%)	61 (3.0%)	62 (3.7%)	109 (3.1%)
Drug overdose	38 (1.9%)	37 (2.0%)	40 (2.0%)	35 (2.1%)	72 (2.0%)
Chest pain	55 (2.8%)	53 (2.8%)	12 (0.6%)	13 (0.8%)	66 (1.9%)
<b>Cardiovascular System</b>	231 (11.8%)	210 (11.1%)	241 (11.9%)	179 (10.8%)	389 (11.0%)
Angina Pectoris	11 (0.6%)	14 (0.7%)	8 (0.4%)	<b>10 (0.6%)</b>	24 (0.7%)
Angina, unstable	27 (1.4%)	21 (1.1%)	71 (3.5%)	58 (3.5%)	109 (3.1%)
Bleeding, postoperative	15 (0.8%)	15 (0.8%)	13 (0.6%)	5 (0.3%)	20 (0.6%)
Cardiac arrest	7 (0.4%)	8 (0.4%)	<b>19 (0.9%)</b>	13 (0.8%)	<b>21 (0.6%)</b>
CVA	13 (0.7%)	6 (0.3%)	15 (0.7%)	12 (0.7%)	18 (0.6%)
Dissection, Coronary Artery	35 (1.8%)	34 (1.8%)	3 (0.1%)	1 (0.1%)	35 (1.0%)
Heart failure	15 (0.8%)	13 (0.7%)	15 (0.7%)	16 (1.0%)	29 (0.8%)
Hypotension	9 (0.5%)	6 (0.3%)	15 (0.7%)	13 (0.8%)	<b>19 (0.6%)</b>
Myocardial infarction	18 (0.9%)	12 (0.6%)	<b>10 (0.5%)</b>	14 (0.8%)	26 (0.7%)
Shock, cardiogenic	20 (1.0%)	16 (0.8%)	28 (1.4%)	17 (1.0%)	26 (0.7%)
Ventricular fibrillation	12 (0.6%)	15 (0.8%)	10 (0.5%)	<b>7 (0.4%)</b>	22 (0.6%)
Ventricular tachycardia	<b>8 (0.4%)</b>	10 (0.5%)	7 (0.3%)	0 (0%)	10 (0.3%)
<b>Digestive System</b>	29 (1.5%)	17 (0.9%)	33 (1.6%)	14 (0.8%)	31 (0.9%)
Hemorrhage, gastrointestinal	11 (0.6%)	2 (0.1%)	9 (0.4%)	0 (0%)	2 (<0.1%)
<b>Endocrine System</b>	3 (0.2%)	0 (0%)	0 (0.0%)	1 (0.1%)	1 (<0.1%)
<b>Hemic &amp; Lymphatic System</b>	6 (0.3%)	6 (0.3%)	8 (0.4%)	4 (0.2%)	10 (0.3%)
<b>Metabolic/Nutritional/Immune System</b>	3 (0.2%)	4 (0.2%)	4 (0.2%)	4 (0.2%)	8 (0.3%)
<b>Musculoskeletal System</b>	6 (0.3%)	10 (0.5%)	9 (0.4%)	4 (0.2%)	14 (0.4%)
<b>Nervous System</b>	<b>15 (0.8%)</b>	6 (0.3%)	12 (0.6%)	11 (0.7%)	17 (0.5%)
<b>Respiratory System</b>	26 (1.3%)	43 (2.3%)	52 (2.6%)	51 (3.1%)	94 (2.6%)
Edema, pulmonary	7 (0.4%)	9 (0.5%)	20 (1.0%)	15 (0.9%)	24 (0.7%)
Pneumonia	5 (0.3%)	<b>10 (0.5%)</b>	9 (0.4%)	8 (0.5%)	18 (0.5%)
<b>Dermatologic System</b>	9 (0.5%)	6 (0.3%)	11 (0.5%)	14 (0.8%)	20 (0.5%)
<b>Special Senses System</b>	2 (0.1%)	1 (0.1%)	0 (0%)	2 (0.1%)	3 (<0.1%)
<b>Urogenital System</b>	22 (1.1%)	22 (1.2%)	13 (0.6%)	12 (0.7%)	34 (1.0%)

a. Data from NDA volume I, Table D-60 and electronic datasets.

The next table shows the incidence of serious adverse events which were felt to possibly, probably, or definitely be related to study drug administration, arranged by body system. Individual SAEs are shown if they occurred with a rate of  $>0.5\%$ . Otherwise, the overall body system incidence rate is shown. The heparin group is not divided due to the small number of events. Shaded rows are those SAEs where the incidence of a given SAE in the heparin group was  $>2$  times or  $<0.5$  times the rate in either the tirofiban alone or tirofiban +heparin groups. A listing of the individual subjects who experienced serious adverse events can be found in appendix 3, section 15.0.

8.1.2 Other serious adverse events (SAEs) in the phase II-III safety database (cont)

Table 8.1.2.2 Serious adverse events considered possibly, probably, or definitely related to study drug administration, collected in the phase II-III safety database<sup>a</sup>.

Body System/ SAE	Tirofiban + Heparin n=1953	Tirofiban n=2032	Heparin n=3546
<b>Total # with SAEs</b>	<b>47 (2.4%)</b>	<b>24 (1.2%)</b>	<b>28 (0.8%)</b>
<b>Body as a whole</b>	8 (0.4%)	2 (0.1%)	5 (<0.1%)
<b>Cardiovascular System</b>	26 (1.3%)	7 (0.3%)	20 (0.6%)
Bleeding, postoperative	8 (0.4%)	1 (0.0%)	2 (<0.1%)
<b>Digestive System</b>	6 (0.3%)	8 (0.4%)	1 (<0.1%)
<b>Hemic/Lymphatic</b>	4 (0.2%)	4 (0.2%)	1 (<0.1%)
<b>Nervous System</b>	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
<b>Respiratory System</b>	2 (0.1%)	0 (0.0%)	1 (<0.1%)
<b>Dermatologic System</b>	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
<b>Special Senses System</b>	0 (0.0%)	0 (0.0%)	1 (<0.1%)
<b>Urogenital System</b>	4 (0.2%)	1 (<0.1%)	0 (0.0%)

a. Data from NDA volume 1.37, Table D-61 and electronic datasets.

### 8.1.3 Clinical adverse events (AEs) from the Phase II-III Tirofiban safety database

The adverse experience tables below present the percentages of subjects having at least one adverse event on treatment during the adverse experience reporting period of the respective protocols (non-serious events through 24 hours after drug cessation; serious adverse events through Day 30 after start of study drug). Only those events which occurred at a rate of  $\geq 1.0\%$  in any of the treatment groups are presented. A subject may be counted more than once if he/she had multiple adverse experiences classified in more than one body system. However, a given patient is counted only once in the overall total and once in any particular body system, regardless of how many clinical adverse experiences were reported in that body system. Similarly, a subject who reported multiple occurrences of the same adverse event appears only once for that particular adverse event.

Adverse events are broken into bleeding and nonbleeding for purposes of review. This comes from the relative incidence and clinical importance of bleeding events in the trials of this NDA. Additionally, as was discussed in section 8.0.4.7 above, the sponsor argues that there is a significant difference in the rates and types of adverse events seen in the trials involving pre-specified use of procedures (PTCA in the RESTORE trial, angiography in the PRISM-PLUS trial). To facilitate this comparison in section 8.2, three 'Heparin' columns will be presented for the bleeding adverse events: Heparin/Procedures; Heparin/No Procedures; and Total Heparin Alone.

The shaded boxes represents AEs where there is  $\geq 2X$  difference between one of the two tirofiban groups and either its respective heparin group, or the total heparin group.

Table 8.1.3.1 **Nonbleeding** adverse events in the phase II-III trials of tirofiban from NDA 20-9 12".

	Tirofiban + Heparin n=1953	Heparin/ Procedures n=1887	Tirofiban n=2032	Heparin/ No Procedures n=1659	Total Heparin <sup>b</sup> n=3546
Subjects with a nonbleeding clinical AE	1545 (79.1%)	1465 (77.6%)	1111 (54.7%)	812 (48.9%)	2277 (64.2%)
Subjects without a nonbleeding clinical AE	408 (20.9%)	422 (22.4%)	921 (45.3%)	847 (51.1%)	1269 (35.8%)
<b>Body as a whole</b>	<b>650 (33.3%)</b>	<b>597 (31.6%)</b>	<b>354 (17.4%)</b>	<b>232 (14.0%)</b>	<b>829 (35.8%)</b>
Asthenia/fatigue	48 (2.5%)	52 (2.8%)	31 (1.5%)	7 (0.4%)	59 (2.3%)
Death	39 (2.0%)	47 (2.5%)	61 (3.0%)	62 (3.7%)	109 (3.1%)
Drug overdose	38 (1.9%)	37 (2.0%)	40 (0.0%)	36 (2.2%)	73 (2.0%)
Edema/swelling	31 (1.6%)	27 (1.4%)	24 (1.2%)	9 (0.5%)	36 (1.0%)
Fever	123 (6.3%)	120 (6.4%)	56 (2.8%)	38 (2.3%)	158 (4.4%)
Hyperthermia	22 (1.1%)	20 (1.1%)	0.4 (0.0%)	0 (0.0%)	20 (0.5%)
Malaise	17 (0.9%)	18 (1.0%)	5 (0.2%)	3 (0.2%)	21 (0.5%)
Pain	23 (1.2%)	26 (1.4%)	16 (0.8%)	2 (0.1%)	28 (0.8%)
Pain, abdominal	102 (5.2%)	86 (4.6%)	60 (3.0%)	35 (2.1%)	121 (3.4%)
Pain, chest	162 (8.3%)	172 (9.1%)	46 (2.3%)	36 (2.2%)	208 (5.9%)
Pain, pelvic	115 (5.9%)	90 (4.8%)	15 (0.7%)	4 (0.2%)	94 (2.6%)
Reaction, vasovagal	40 (2.0%)	20 (1.1%)	12 (0.6%)	4 (0.2%)	24 (0.5%)
<b>Cardiovascular System</b>	<b>664 (34.0%)</b>	<b>644 (34.1%)</b>	<b>468 (23.0%)</b>	<b>325 (19.6%)</b>	<b>969 (27.3%)</b>
Angina, pectoris	26 (1.3%)	27 (1.4%)	9 (0.4%)	11 (0.7%)	38 (1.1%)
Angina, unstable	27 (1.4%)	21 (1.1%)	71 (3.5%)	57 (3.4%)	78 (2.2%)
Atrial fibrillation	18 (0.9%)	19 (1.0%)	14 (0.7%)	15 (0.9%)	34 (1.0%)
Bradycardia	73 (3.7%)	52 (2.8%)	20 (1.0%)	23 (1.4%)	75 (2.1%)
Dissection, coronary artery	88 (4.5%)	83 (4.4%)	4 (0.2%)	3 (0.2%)	86 (2.4%)
Heart failure	33 (1.7%)	35 (1.9%)	38 (1.9%)	46 (2.8%)	81 (2.3%)
Hypertension	22 (1.1%)	19 (1.0%)	9 (0.4%)	4 (0.2%)	23 (0.6%)
Hypotension	150 (7.7%)	153 (8.1%)	74 (3.6%)	39 (2.4%)	192 (5.4%)
Infused vein complication	40 (2.0%)	41 (2.2%)	46 (2.3%)	16 (1.0%)	57 (1.6%)
Pain, catheter, cardiac	16 (0.8%)	24 (1.3%)	6 (0.3%)	1 (0.1%)	25 (0.7%)
Peripheral pulse, decreased	20 (1.0%)	12 (0.6%)	7 (0.3%)	1 (0.1%)	13 (0.4%)
Phlebitis/thrombophlebitis	10 (0.5%)	13 (0.7%)	23 (1.1%)	15 (0.9%)	28 (0.7%)
Premature ventricular contractions	32 (1.6%)	40 (2.1%)	17 (0.8%)	10 (0.6%)	50 (1.4%)
Shock, cardiogenic	20 (1.0%)	16 (0.8%)	28 (1.4%)	18 (1.1%)	34 (1.0%)
Ventricular tachycardia	36 (1.8%)	58 (3.1%)	24 (1.2%)	10 (0.6%)	68 (1.9%)

a. Data from NDA volume 1.2, Tables 2-37 and electronic datasets.

b. Includes all subjects from Heparin/No procedures and Heparin/Procedures groups.