Table of Contents

Volume 1

Volume 2

TIROFIBAN

Combined Medical & Statistical Review
Aggrastat® Injection
(Tirofiban)

NDA #20-912

Division of Cardiovascular and Renal Drugs

March 30, 1998

Table of Contents

a. A detailed tables of contents for this trial appears below.

Table of Contents (cont)

Table of Contents (cont)

Tables of Contents For PRISM-PLUS, PRISM, and RESTORE Trials

Tables of Contents For
PRISM-PLUS, PRISM, and RESTORE Trials (cont)

Tables of Contents for Key Data-Tables

Tables of Contents for Key Data-Tables (cont)

6.2.1.13 Safety Outcomes

The deaths, serious adverse events, and adverse events by body system will be considered in section 8.1 and 8.2. The section below will comment on the following specific safety parameters from the RESTORE trial: deaths; subject discontinuations; bleeding AEs; and thrombocytopenia. The first table summarizes the adverse clinical events that occurred in the PRISM-PLUS trial. The combination 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 6.2.1.13.1 Clinical adverse experience (AE) summary from the PRISM-PLUS trial[a].

Clinical event	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	p value T+H vs. H[c]
With any AE	289 (83.8%)	654 (84.7%	657 (82.4%)	0.25
Without any AE	56 (16.2%)	119 (15.3%)	140 (17.6%)	
With Serious AE (SAE)	77 (22.3%)	180 (23.3%)	174 (21.8%)	0.51
With drug-related AE[b]	134 (38.8%)	273 (35.3%)	203 (25.5%)	<0.001
With serious and drug-related AEs	5 (1.4%)	18 (2.3%)	8 (1.0%)	0.048
Discontinued due to an AE	9 (2.6%)	42 (5.4%)	20 (2.5%)	0.004
Discontinued due to a bleeding AE	5 (0.4%)	24 (3.1%)	7 (0.9%)	0.002
Discontinued due to lab AE	2 (0.6%)	5 (0.6%)	5 (0.6%)	0.99
Deaths[d]	21 (6.1%)	30 (3.9%)	39 (4.9%)	0.39

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 5 subjects who died after 30 days.

6.2.1.13.1 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-PLUS trial: deaths; subject discontinuations; bleeding AEs; and thrombocytopenia.

6.2.1.13.2 Comments on Specific Safety Parameters

Deaths

Through 30 days of follow-up, 85 subject deaths had been reported in the PRISM-PLUS trial. Five other deaths were reported to the sponsor shortly after the 30 days, and were included in their safety database. At the end of the 180 day follow-up, there were 134 reported deaths. The table below summarizes these deaths by treatment group and time of reporting. The highest % of deaths was in the tirofiban alone arm, which was discontinued for this reason.

Table 6.2.1.13.2.1 (from table 8.1.1.1d. 1) Deaths in the PRISM-PT.1 JS trial[a].

Time of Follow-up	Tirotiban alone n=345	Tirotiban + Heparin n=773	Heparin alone n=797	Total
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%)	8.5 (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).
Further details of the deaths will be examined in section 8.1.

Subject discontinuations

As shown above, more subjects in the tirofiban +heparin group were discontinued for bleeding AEs. The next table summarizes the major causes for subject discontinuations in the PRISM-PLUS trial. These were more frequent in the tirofiban +heparin group (5.4%) than in the heparin group (2.5%, p=0.004). This difference was primarily due to increased bleeding AEs (see table 6.2.1.13.1). A full listing of the discontinuations is found in appendix 4, section 16.0.

Table 6.2.1.13.2.2 Significant clinical AEs leading to discontinuation in the PRISM-PLUS trial[a].

	Tirofiban alone n=345	Tirofiban + Heparin n=773	Heparin alone n=797	p value T+H vs. H[b]
Any Adverse Experience	9 (2.6%)	42 (5.4%)	20 (2.5%)	0.004
Body as a Whole/Site Unspecified)	0 (0%)	0 (0%)	1 (0.1%	0.99
Cardiovascular System	3 (0.9%)	20 (2.6%)	10 (1.3%)	0.065
Bleeding, postoperative	1 (0.3%)	5 (0.6%)	0 (0%)	0.029
Dissection, coronary artery	0 (0%)	5 (0.6%)	0 (0%)	0.029
Hematoma	0 (0%)	3 (0.4%)	2 (0.3%)	0.68
Digestive System	3 (0.9%)	6 (0.8%)	2 (0.3%)	0.17
GI hemorrhage	0 (0%)	3 (0.4%)	0 (0%)	0.12
Hematologic/ Lymphatic	1 (0.3%)	6 (0.8%)	1 (0.1%)	0.066
Thrombocytopenia	1 (0.3%)	5 (0.6%)	1 (0.1%)	0.12
Urogenital System	1 (0.3%)	7 (0.9%)	3 (0.4%)	0.22

a. Data from NDA vol. 1.42, ref 5, table 35 and electronic datasets.
b. p value calculated using chi square test by the sponsor.

Table 6.2.1.13.2.3 Laboratory AEs, including AEs leading to discontinuation, in the PRISM-PLUS trial*.

	Tirofiban Alone n=345	Tirofiban + Heparin n=773	Heparin Alone n=797	p value T+H vs. H[b]
With any laboratory AE	144 (41.7%)	292 (37.8%)	276 (34.6%)	0.21
With drug-related laboratory AE[c]	83 (24.1%)	188 (24.3%)	150 (18.8%)	0.008
With any serious laboratory AE	0 (0.%)	0 (0.%)	3 (0.4%)	0.25
With serious drug-related laboratory AE	0 (0%)	0 (0%)	1 (0.1%)	0.99
Discontinued due to a laboratory AE	2 (0.6%)	5 (0.6%)	5 (0.6%)	0.99
Discontinued due to bleeding lab AE	1 (0.3%)	3 (0.4%)	3 (0.4%)	0.99

a. Data from NDA vol. 1.42, ref 5, table 36 and electronic datasets
b. p value calculated using chi square test by the sponsor.
c. Drug-related per individual investigator.

Bleeding AEs

Per the sponsor, the bleeding in the tirofiban +heparin group was more frequent and 'somewhat more severe.' Overall, the combination group experienced oozing 56% and moderate or worse 9.5%, compared with 42.8% and 6.5% respectively for the heparin alone group (p<0.001). This excess bleeding was seen with IV sites, catheterization sites, nosebleeds, GU/hematuria and 'other' bleeding sites (primarily post-op bleeding).

Table 6.2.1.13.2.4 Bleeding AEs in the PRISM-PLUS trial[a].

	Tirofiban Alone n=345	Tirofiban + Heparin n=773	Heparin Alone n=797	p value T+H vs. H[b]
Any bleeding AE	134 (38.8%)	340 (44.0%)	456 (57.2%)	<0.001
No bleeding complication	210 (61%)	433 (56%)	341 (42.7%)	

a. Data from NDA vol. 1.42, ref 5, table 40 and electronic datasets.
b. p value calculated using chi square test by the sponsor.

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 3 1 (4%) of the tirofiban +heparin groups and 24 (3.5%) of the heparin group (p=0.34). TIMI-class major bleeds occurred in 11 (1.4%) of the combination and 6 (0.8%) of the heparin groups (p=0.23).

Bleeding **AEs (cont)**

Table 6.2.1.13.2.5 Major bleeding AEs grouped by severity in the PRISM-PLUS trial[a].

	Tirofiban Alone n=345	Tirofiban + Heparin n=773	Heparin Alone n=797	p value T+H vs. H[b]
Major Bleeding (protocol defined)[c]				
No	327 (94.8%)	742 (96.0%)	773 (97.0%)	0.34
Yes	18 (5.2%)	31 (4.0%)	24 (3.0%)	
TIMI Bleeding: any				0.077
Major	9 (2.6%)	11 (1.4%)	6 (0.8%)	0.23
Minor	35 (10.1%)	81 (10.5%)	64 (8.0%	
Loss/ No site identified	2 (0.6%)	5 (0.6%)	7 (0.9%)	

a. Data from NDA vol. 1.42, ref 5, table 40 and electronic datasets.

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

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 bleeding adverse events is shown below grouped by site of bleeding. Life-threatening bleeds occurred at a similar frequency in the two groups (0.8 vs. 0.6%), and no intracranial or retroperitoneal bleeds occurred in the combination group. Compared with the heparin group, there was significantly more overall bleeding, and bleeding for the following sites in the combination group: IVs; catheters; nasal; and GI.

Table 6.2.1.13.2.6 Major bleeding grouped by bleeding site AEs in the PRISM-PLUS trial[a].

	Tirofiban Alone n=345	Tirofiban + Heparin n=773	Heparin Alone n=797	p-value (T +H vs. H)[b]
Any site				<0.001
Oozing	75 (21.7%)	171 (22.1%)	149 (18.7%)	
Mild	97 (28.1%)	188 (24.3%)	139 (17.4%)	
Moderate	24 (7.0%)	50 (6.5%)	36 (4.5%)	
Severe	6 (1.6%)	17 (2.2%)	11 (1.4%)	
Life-threatening	8 (2.3%)	6 (0.8%)	5 (0.6%)	
IV site				0.049
Oozing	24 (7.0%)	59 (7.6%)	47 (5.9%)	
Mild	14 (4.1%)	36 (4.7%)	31 (3.9%)	
Moderate	1 (0.3%)	7 (0.9%)	2 (0.3%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	0 (0%)	
Catheter site				0.016
Oozing	56 (16.2%)	102 (13.2%)	82 (10.3%)	
Mild	45 (13.0%)	70 (9.1%)	60 (7.5%)	
Moderate	17 (4.9%)	14 (1.9%)	14 (1.8%)	
Severe	2 (0.6%)	7 (0.9%)	3 (0.4%)	
Life-threatening	2 (0.6%)	0 (0%)	0 (0%)	
Oral				**0.096**
Oozing	3 (0.9%)	**3 (0.4%)**	**2 (0.3%)**	
Mild	3 (0.9%)	**6 (0.8%)**	0 (0%)	
Moderate	0 (0%)	**1** (0.1%)	**2 (0.3%)**	
Severe	0 (0%)	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	0 (0%)	
Nasal				<0.001
Oozing	**25 (7.2%)**)	28 (3.6%)	13 (1.6%)	
Mild	18 (5.2%))	31 (4.0%)	3 (0.4%)	
Moderate	1 (0.3%)	2 (0.3%)	0 (0%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	0 (0%)	

6.2.1.13.2 Comments on Specific Safety Parameters

Bleeding AEs (cont)

Table 6.2.1.13.2.6 Major bleeding grouped by bleeding site AEs in the PRISM-PLUS trial (cor

	Tirofiban Alone n=345	Tirofiban + Heparin n=773	Heparin Alone n=797	p-value (T +H vs. H)[b]
GU/ Hematuria				<0.001
Oozing	23 (6.7%)	59 (7.6%)	47 (5.9%)	
Mild	32 (9.3%)	69 (8.9%)	42 (5.3%)	
Moderate	3 (0.9%)	10 (1.3%)	6 (0.8%)	
Severe	0 (0%)	2 (0.3%)	1 (0.1%)	
Life-threatening	0 (0%)	0 (0%)	0 (0%)	
GI				<0.001
Oozing	21 (6.1%)	42 (5.4%)	27 (3.4%)	
Mild	15 (4.3%)	33 (4.3%)	20 (2.5%)	
Moderate	3 (0.9%)	10 (1.3%)	2 (0.3%)	
Severe	0 (0%)	2 (0.3%)	0 (0%)	
Life-threatening	2 (0.6%)	2 (0.3%)	0 (0%)	
Hemoptysis				0.15
Oozing	3 (0.9%)	6 (0.8%)	3 (0.4%)	
Mild	2 (0.6%)	3 (0.4%)	1 (0.1%)	
Moderate	0 (0%)	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Life-threatening	0 (0 %)	0 (0%)	0 (0%)	
Intracranial				NA[b]
Oozing	0 (0%)	0 (0%)	0 (0%)	
Mild	0 (0%)	0 (0%)	0 (0%)	
Moderate	0 (0%)	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Life-threatening	0 0 %)	0 (0%)	0 (0%)	
Retroperitoneal				0.33
Oozing	0 (0%)	0 (0%)	0 (0%)	
Mild	0 (0%)	0 (0%)	0 (0%)	
Moderate	1 (0.3%)	0 (0%)	0 (0%)	
Severe	1 (0.3%)	0 (0%)	0 (0%)	
Life-threatening	0 (0%)	0 (0%)	1 (0.1%)	
Other				0.009
Oozing	11 (3.2%)	21 (2.7%)	8 (1 .O%)	
Mild	9 (2.6%)	16 (2.1%)	8 (1.0%)	
Moderate	2 (0.6%)	8 (1.0%)	10 (1.3%)	
Severe	3 (0.9%)	5 (0.6%)	3 (0.4%)	
Life-threatening	4 (1.2%)	4 (0.5%)	3 (0.4%)	

ata from NDA vol. 1.42, ref 5, ta 40 and electronic datasets. Definitions of categories can be found in section 5.3.

b. p value calculated using chi square test by the sponsor. NA, no statistical analysis due to small subject numbers

INTEGRATED MEDICAL AND STATISTICAL REVIEW
OF NEW DRUG APPLICATION #20-912

NDA: #20-912
DRUG NAME: Tirofiban Hydrochloride (MK-0383)
TRADE NAME: Aggrastat®
FORMULATION: For intravenous injection
SPONSOR: Merck Research Laboratories
TYPE OF DOCUMENT: New Drug Application

MEDICAL REVIEWER: Douglas C. Throckmorton, M.D.
STATISTICAL REVIEWER: James Hung, Ph.D.

PROPOSED INDICATION: Aggrastast (tirofiban) is indicated, 'in combination with heparin, to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction (UAP/NQWMI), including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated.'

DATE OF NDA SUBMISSION: 10.31.97
DATE RECEIVED BY FDA: 10.3 1.97
DATE ASSIGNED: 11.13.97
DATE REVIEW COMPLETED: 3.30.98

0.0 Overall NDA Summary

Aggrastat (tirofiban), an inhibitor of platelet aggregation, is proposed for use following unstable angina or non-Q-wave myocardial infarction (UAP/NQWMI) to prevent further cardiac ischemic events. In support of the proposed indication, the sponsor submitted this NDA, including the results of three phase III trials: PRISM-PLUS; PRISM; and RESTORE. Two of these trials (PRISM and PRISM-PLUS) were conducted in a population of subjects with UAP/NQWMI. The RESTORE trial was conducted in subjects with UAP or acute MI undergoing angioplasty or atherectomy. A list of the abbreviations used in this review is found in appendix one.

PRISM-PLUS Trial

The PRISM-PLUS trial enrolled 1915 subjects with UAP/NQWMI, presenting within 12 hours of their last episode of prolonged, repetitive, or post-infarction angina1 pain. They were randomly assigned to receive one of three therapies: tirofiban-alone; tirofiban +heparin; and heparin-alone. Subjects also received aspirin if tolerated. Subjects were then followed for the occurrence of clinical events. The tirofiban-alone group was stopped for safety concerns after enrolling 345 subjects. The tirofiban +heparin and heparin-alone groups were continued, enrolling 773 and 797 respectively.

In the PRISM-PLUS trial the pre-specified, the primary endpoint was the incidence of refractory cardiac ischemic conditions (RIC), recurrent myocardial infarction (MI), or death from any cause within 7 days of the start of study drug. The proportions of subjects who met the composite endpoint by 7 days was 100/773 (12.9%) in the tirofiban +heparin group and 143/797 (17.9%) in the heparin-alone group. This difference between treatments has an odds ratio of 0.660, which represents a 33% risk reduction for an event for the tirofiban group (p=0.004).

Secondary endpoints were the incidence of the same combined endpoint at 48 hours and 30 days. At both time points (48 hours and 30 days), the tirofiban +heparin group had a significantly lower incidence of the combined endpoint when compared with heparin only. 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. A nominally 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. Several subgroup analyses also found a trend towards benefit favoring tirofiban +heparin.

PRISM-PLUS had an angiographic substudy which assessed the acute (<96 hours) effect of tirofiban on the angiographic progression of disease. Using three separate indices to assess patency, the sponsor concluded that tirofiban +heparin had a significant effect to enhance short-term coronary artery patency, when compared with heparin alone.

From a safety standpoint, subjects in the tirofiban +heparin group had significantly more bleeding, including more nasal, catheter-site, GI and GU bleeding. The incidence of TIMI-defined major bleeding was as follows: tirofiban-alone, 2.6%; tirotiban +heparin, 1.4%; and heparin-alone, 0.8%. Life-threatening bleeds occurred at an equal frequency in the tirofiban +heparin and heparin-alone groups. There was also a strong trend towards a higher incidence of thrombocytopenia in the tirofiban +heparin group, compared with heparin-alone (2.5% vs. 1.2%, p=0.056).

The decision to drop the tirofiban-alone arm early in the trial due to concerns about apparent increased mortality was likely a reflection of inadequate numbers of events, and does not represent a signal for true increased mortality in the tirofiban-alone group. This statement is supported by the PRISM trial, where there was a nominally significant survival advantage for the tirofiban-alone group at the end of 30 days, when compared with heparin-alone.

PRISM Trial

The PRISM trial enrolled 3232 subjects with UAP/NQWMI, presenting within 24 hours of their last prolonged, repetitive, or post-infarction anginal episode, who were randomly assigned treatment with either heparin or tirofiban (1616 subject in each arm). Subjects also received ASA if tolerated. 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 incidence of the same endpoint at 7 and 30 days were pre-specified secondary and supportive endpoints respectively. The proportions of subjects who met the composite endpoint at 48 hours was 6111616 (3.8%) in the tirofiban group and 9 1/1 6 16 (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 tirotiban group (p=0.014).

For the secondary and supportive endpoints, there was a non-significant trend, favoring tirofiban. For the components of the primary endpoint, while there is a trend favoring the tirofiban group, after 48 hours the only nominally significant effect of tirotiban was on mortality at 30 days (but not at 48 hours or 7 days).

From a safety standpoint, there was a significant increase in the incidence of bleeding in the tirofiban group compared with heparin at the following sites: oral; nasal; GU; GI; pulmonary (hemoptysis); other; and unknown. The incidence of TIMI-defined major bleeding was as follows: tirofiban alone, (0.4%); heparin, (0.4%%). Life-threatening bleeds occurred at a similar frequency in the two groups (0.6 vs. 0.4%).

PRISM Trial (cont)

Thrombocytopenia was more common in the tirofiban group than in the heparin group, regardless of the definition used to detect thrombocytopenia. Seventeen (1.1%) of the tirofiban group had at least one platelet count <90,000/mm^3, compared with 7 (0.4%) of the heparin group (p=0.042).

RESTORE Trial

The RESTORE trial enrolled 2141 subjects undergoing PTCA within 72 hours of presentation with UAP or acute MI (Q-wave and non-Q-wave MI). Subjects were randomized to receive either tirofiban or placebo for the 48 hours just prior to, during, and after PTCA. All subjects also received heparin and ASA if tolerated. They were then followed for clinical endpoints. 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 proportions of patients who met the composite endpoint by 30 days was 11011071 (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).

There was a non-significant trend favoring tirofiban for the incidence of most individual components of the composite endpoint, 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.

From a safety standpoint, the tirofiban +heparin group had significantly more bleeding than did the heparin alone group. These bleeding AEs occurred in the cardiovascular system, related to procedures, as well as the GI and GU systems. The incidence of TIMI-defined major bleeding was as follows: tirofiban +heparin group, 2.2%; and placebo (+ heparin) group, 1.6%. This included 6 retroperitoneal bleeds in the tirofiban (+heparin) group (0.56%) versus 3 in the placebo (+heparin group) (0.28%). More subjects in the tirofiban (+heparin) group received transfusion of packed RBCs (4.0%) than in the placebo (+heparin) group (2.4%), p=0.049.

Thrombocytopenia was not significantly more common in the tirofiban +heparin group than in the heparin alone group (1 .l% vs. 0.8%).

Overall Safety from the Phase II-III database for Tirofiban

At the end of 30 days, the incidence of death in the three treatment groups, from the phase III trials, was a follows: tirofiban alone: 58/2032 (2.85%); tirofiban +heparin, 37/1953 (1.89%); and heparin alone, 103/3546 (2.90%).

Overall Serious Adverse Events (SAEs) occurred with equal frequency in the tirofiban-alone group (1 8%), the tirofiban +heparin group (20%); and the heparin-alone group (18%). Gastrointestinal hemorrhage as an SAE occurred more frequently in the tirofiban-alone group (0.4%), and tirofiban +heparin group (0.6%), compared with heparin alone (0.1%).

While non-bleeding adverse events (AEs) occurred with equal frequency in the treatment groups, bleeding AEs occurred more frequently in the tirofiban +heparin group (52.3%) than in either the tirofiban-alone group (20.9%) or the heparin-alone group (24.7%). These bleeding events were most common in those subjects who underwent procedures during administration of tirofiban and/or heparin (see PRISM-PLUS and RESTORE trials). As a result of these AEs, more subjects in the tirofiban +heparin group were discontinued for a bleeding AE (3.6%) than in the tirofiban-alone group (1.1%), or the heparin-alone group (0.7%).

There was an increase in minor bleeding in the tirofiban +heparin group, compared with the heparin-alone group. Excess bleeding occurred at several sites, including GI, GU, oral, and respiratory track.

A higher percentage of tirofiban +heparin subjects required transfusion of PRBCs than the comparator heparin group (3.6% vs. 2.4%). The tirofiban-alone group also had a higher frequency of any transfusion than the heparin-alone group (2.4% vs. 1.2%).

Thrombocytopenia was more common in the tirofiban groups. For the overall phase II-III database, the rates of thrombocytopenia (<90,000/mm^3) were 1.5% in the tirofiban + heparin group, and 1.2% in the tirofiban-alone group, versus 0.6% for all heparin-alone subjects. The incidence of severe thrombocytopenia (<20,000/mm^3) was as follows: 4/2032 (0.2%) in the tirofiban alone group; 1/1953 in the tirofiban +heparin (0.1%); and 213546 (0.1%) in the heparin alone group.

1.0 Materials Utilized in Review

1.1 Materials from NDA/IND

I. NDA #20-912: volumes 1.2; 1.8-1.72

2. Tirofiban computer-assisted NDA (CANDA), including case report forms (CRFs). The CRFs were submitted electronically by the sponsor in the following categories:

a. Deaths.

b. Discontinued from therapy due to an adverse experience.

b1. Discontinued due to an adverse experience.

b2. Discontinued due to a clinical endpoint.

c. Discontinued from therapy for any other reason.

d. Serious adverse experiences.

e. Endpoints adjudicated by committee for patients that are not included in any previous category. Patients in the RESTORE Study that died after day 30 are also included in this category.

f. PRISM-PLUS: 6-month investigator-reported endpoints that occurred between days 31-180 for patients that are not included in any previous category. Patients in PRISM-PLUS that died on days 31-180 will appear in this category.

3. Two supplemental listings of all patients who reached a clinical endpoint.

a. Supplement A is a listing of all patients who experienced a clinical, endpoint adjudicated by committee, excluding PRISM-PLUS 6-month follow-up data. The category for which the patient qualified is also provided in the supplement.

b. Supplement B is a listing of all PRISM-PLUS patients who experienced an endpoint during the 6-month follow-up period (days 3 l-180). The category for which the patient qualified is also provided in the supplement. Excluded from all listings are patients who never received study drug or whose event occurred prior to receiving study drug.

4. IND

5. Approved package insert for Reopro (Abciximab), revised 11.4.97.

6. Proposed package insert for Plavix (clopidogrel), submitted 11.3.97.

7. Primary Medical Officer review for Plavix (clopidogrel): NDA 20-839.

8. NDA 20-718 (Integrilin).

9. Primary Medical Officer review for PURSUIT trial (Integrilin): NDA 20-718.

10. Published results from the EPIC, EPILOGUE, CAPTURE, & IMPACT-II trials(l-5).

1.2 Related Reviews, Consults for the NDA

No outside reviews or consultants were obtained as part of this NDA review.

1.3 Other Resources

No separate consultations, including outside experts or advisory committee proceedings, were obtained during this NDA review. The literature review is included in section 5.2.

2.0 Background

The acute coronary ischemic syndromes of unstable angina and myocardial infarction share a common underlying pathophysiology: disruption of atherosclerotic plaque in a coronary artery. Plaque fissuring or rupture results in exposure of thrombogenic material to circulating blood, leading to clot formation with partial or complete occlusion of coronary blood flow, leading to myocardial ischemia or infarction. Similarly, balloon inflation during percutaneous transluminal coronary angioplasty (PTCA) results in rupture of atherosclerotic plaque that can lead to clot formation and acute closure of the coronary artery. Coronary stent placement also provides a thrombogenic surface on which recurrent thromboses can form. Regardless of the cause of the thrombosis (whether ruptured plaque or artificial surface), the severity and dynamic nature of the resultant clinical syndrome is dependent to a large extent on the extent and timing of clot formation. Platelet activation, adhesion, and aggregation represent the critical initiating steps in the formation of the arterial thrombus. Thus, effective antithrombotic therapy, and in particular, pharmacological antagonism of platelet function, has been central to the management of patients presenting with acute coronary ischemic syndromes and patients undergoing PTCA. Standard antithrombotic pharmacotherapy, consisting of heparin and aspirin, reduces but does not eliminate the clinical sequelae of these syndromes. A recent meta-analysis of trials of unstable angina suggests that heparin plus aspirin reduces the relative risk of subsequent early death or myocardial infarction by 33% compared to aspirin alone(6). However, many subjects presenting with acute coronary ischemic syndromes continue to have angina refractory to standard antithrombotic and antianginal therapy(7). Furthermore, up to 11% of patients receiving standard antithrombotic therapy will die or have a recurrent myocardial infarction over the subsequent 30 days, and up to 15% of patients initially controlled on standard antithrombotic therapy will have another episode of myocardial ischemia within the same hospitalization. Patients who have recurrent myocardial ischemia are at higher risk of recurrent myocardial infarction or death. These data suggest that improved antithrombotic therapy could further reduce adverse cardiac outcomes in patients presenting with this acute coronary ischemic syndrome.

Over the past few years, substantial progress has been made in understanding the molecular and cellular biology of the platelet. One of the seminal accomplishments of this work has been the identification of the binding of fibrinogen to the platelet glycoprotein (GP) IIb/IIIa receptor as the final common pathway for platelet aggregation. Platelet activation by thrombogenic substrates induces a conformational change in the GP IIb/IIIa receptor resulting in a marked increase in affinity for fibrinogen. Bound fibrinogen crosslinks platelets resulting in platelet aggregation]. Because of its critical role in platelet aggregation and thrombus formation, the GP IIb/IIIa receptor is an attractive target for antithrombotic therapy(8). Several peptide and nonpeptide antagonists of the GP IIb/IIIa receptor, including abciximab and tirofiban, have been developed recently for intravenous use. These products are reviewed in section 2.2 below. Of these, abciximab, a chimeric monoclonal antibody fragment, and clopidogrel, and oral GP IIb/IIIa receptor inhibitor, are currently marketed. Abciximab has been evaluated in three trials for prevention of acute thrombotic complications following percutaneous coronary angioplasty (PTCA) (EPIC, EPILOG, and CAPTURE)(1-3). These trials provide evidence for the utility of abciximab, given with heparin and aspirin, in reducing early, acute cardiac ischemic events related to abrupt closure directly associated with PTCA. Pretreatment of patients with refractory unstable angina with 18 to 24 hours of abciximab, heparin, and aspirin before angioplasty has also been shown to reduce cardiac ischemic complications associated with the procedure(2). Clopidogrel has been evaluated in the CAPRIE study in subjects with established atherosclerosis(9). Administration of clopidogrel for 1 to 3 years to subjects with established atherosclerosis was slightly more effective than aspirin (ASA) in reducing the incidence of recurrent vascular events.

2.1 Indication

Tirofiban has one proposed indications. Per the proposed labeling, 'AGGRASTAT, in combination with heparin, is indicated to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated.'

2.2 Important Information from Related **INDs** and **NDAs**

Two other approved drugs work by inhibiting platelet aggregation via interaction with the GP IIb/IIIa platelet receptor: abciximab (Reopro) and clopidogrel (Plavix). Another product, eptifibatide (Integrilin) has been submitted for approval. A comparison of these three products with tirofiban (Aggrastat) is in the table below.

Table 2.2.1 Comparison of Tirofib with other platelet aggregation inhibitors.

Drug	Formulation/ Mechanism of Action	Proposed/ **approved** population	**Proposed/ approved indications**
Reopro (Abciximab)	**IV** --monoclonal antibody to the GP IIb/IIIa[c] platelet receptor prevents platelet aggregation --monoclonal antibody	Subjects undergoing PTCA who are at high risk for abrupt coronary occlusion after PTCA: 1. Acute Q-wave MI 2. Non-Q-wave Ml or unstable angina not responding to therapy[b] 3. Other high-risk clinical/ morphological characteristics	Reduction of cardiac ischemic events (death, myocardial infarction (MI) or need for urgent revascularization)
Plavix (Clopidogrel)	**Oral** --prevents ADP binding to the GP IIb/IIIa platelet receptor and platelet aggregation	Subjects with recent MI/Stroke or established PVD"	Reduction of atherosclerotic events (new ischemic stroke, new MI, or vascular death)
Integrilin (Eftifibatide)	**IV** --prevents fibrinogen binding to GP IIb/IIIa platelet receptor and platelet aggregation	Subjects with acute non-Q-wave Ml or unstable angina	Reduction in the rate of death and/or MI
Aggrastat (Tirofiban)	**IV** --prevents fibrinogen binding to GP IIb/IIIa platelet receptor and platelet aggregation --non-peptide antagonist	Subjects with the following: 1. Acute non-Q-wave MI or unstable angina, including those undergoing PTCA or atherectomy	Prevention of cardiac ischemic events (death, MI or need for cardiac intervention)

a. PVD = peripheral vascular disease

b. Reopro **is** indicated 'for subjects with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention in planned within 24 hours.' **In this case,** therapy with Reopro is indicated for up to 24 hours, 'concluding one hour after the percutaneous coronary intervention.'

c. GP: glycoprotein.

2.2.1 Efficacy issues identified from related **INDs** and **NDAs**

Four drugs that work by inhibiting platelet aggregation via interaction with the IIb/IIIa platelet receptor have been submitted as NDAs: Reopro (abciximab); Plavix (clopidogrel); Integrilin [eptifibitide); and Aggrastat (tirofiban). Reopro and Plavix are approved for use. Integrilin and Aggrastat have been submitted as NDAs to the Division of Cardio-Renal Drug Products. Three of these drugs (Reopro, Integrilin, and Aggrastat) either have received or have proposed claims for the treatment of UAP/NQWMI. These drugs are compared in section 19.0, appendix #7 (Efficacy Summary for Reopro, Integrilin, and Plavix). Where relevant, the results will also be integrated into section 7.0 (Integrated Review of Efficacy).

2.2.2 Safety issues identified from related INDs and NDAs

NDAs and published materials for the following drugs were examined to identify safety concerns to be addressed in this review: abciximab (Reopro); eptifibatide (Integrilin); and clopidogrel (Plavix). Based on this review, the following adverse events were identified as being potentially linked to the administration of one or more of these compounds: increased bleeding; thrombocytopenia; and neutropenia. All three of these adverse events were specifically examined in the tirofiban database, and the results appear in the integrated safety summary (Increased bleeding, sections 8.1.7.1 and appendix 11, section 23.0; Thrombocytopenia, section 8.1.7.2; Neutropenia, section 8.1.7.3). A summary of the occurrence of the adverse events in the relevant other drugs is included in each section. For instance, the rate of major bleeding and transfusion from both the Reopro and Integrilin databases are summarized, to aid in comparison with the tirofiban data.

2.3 Administrative History

6.20.94 & 1.26.96	End of Phase II meeting with Division of GI and Coagulation Drug Products (HFD-180).
6.4.97	Transfer of IND from HFD-180 to Division of Cardio-Renal Drug Products (HFD-110).
6.23.97	Pre-NDA meeting with the Division of Cardio-Renal Drug Products (HFD-110).
10.3 1.97	Filing of NDA with the Division of Cardio-Renal Drug Products (HFD-1 10).
3.11.98	Submission of revised labeling for tirofiban to the HFD-110.

2.4 Proposed Labeling

--from revised labeling, submitted 3.11.98.

2.4.1 Proposed indications

Aggrastat, in combination with heparin, is indicated to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated.

2.4.2 Proposed contraindications

Aggrastat is contraindicated in patients who are hypersensitive to any component of the product. Since inhibition of platelet aggregation increases the risk of bleeding, Aggrastat is contraindicated in patients with active internal bleeding; a history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm; and in patients who developed thrombocytopenia following prior exposure to Aggrastat.

Aggrastat should be used with caution in the following patients:

I. recent (<1 year) bleeding including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance.
2. known coagulopathy, platelet disorder, or history of thrombocytopenia.
3. platelet count <1 50,000 cells/mm^3.
4. history of cerebrovascular disease within 1 year.
5. major surgical procedure or severe physical trauma within 1 month.
6. history, symptoms, or findings suggestive of aortic dissection.
7. severe uncontrolled hypertension (systolic BP >180 mmHg and/or diastolic BP >110 mmHg).
8. acute pericarditis.
9. hemorrhagic retinopathy.

2.4.3 Proposed dosing schedule

Aggrastat is recommended for use with a calibrated infusion device. Care should be taken to avoid a prolonged loading infusion. Care should also be taken in calculating the bolus dose and infusion rates based on patient weight. In clinical studies patients received aspirin, unless contraindicated.

Unstable Angina Pectoris Or Non-O-Wave Mvocardial Infarction

Aggrastat should be administered intravenously, in combination with heparin, at the initial infusion rate of 0.4 μg/kg/min for 30 minutes. Upon completion of the initial infusion, Aggrastat should be continued at a maintenance infusion rate of 0.1 μg/kg/min.

The following instructions should be used to calculate the infusion rates for Aggrastat:

1. Maintenance infusion rate (ml/hour): multiply the patient's weight in kg by 0.12 and infuse this number of ml per hour. Mix well before administration.

2. Loading infusion rate: multiply the maintenance infusion rate by 4. The calculated ml/hour should be administered at this rate for 30 minutes.

Note: When calculating the infusion rates, any given decimal place ≥ 0.5 ml should be rounded upward.

Patients With Severe Renal Insufficiency

The dosage of Aggrastat should be decreased by 50% in patients with severe renal insufficiency (creatinine clearance <30 ml/min).

Other Patient Populations

No dosage adjustment is recommended for elderly patients.

2.4.4 Proposed Language Regarding Drug Interactions, Special Safety Concerns And Populations, And Monitoring

2.4.4a Drug interactions

Aggrastat has been studied on a background of aspirin and heparin. The use of Aggrastat, in combination with heparin and aspirin, has been associated with an increase in bleeding compared to heparin and aspirin alone (see precautions below). Caution should be employed when Aggrastat is used with other drugs that affect hemostasis (e.g., warfarin).

Aggrastat has been used concomitantly in clinical studies with beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory agents (NSAIDS) and nitrate preparations without evidence of clinically significant adverse interactions.

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 drug. There were no clinically significant interactions of these drugs on the plasma clearance of tirofiban: acebutolol, acetamiuophen, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosamide, glyburide, heparin, insulin, isosorbide, levothyroxine, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, omeprazole, oxazepam, potassium chloride, propranoiol, ranitidine, simvastatin, sucralfate and temazepam.

2.4.4b Precautions

a. Bleeding Precautions

Because Aggrastat inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis. The safety of Aggrastat when used in combination with thrombolytic agents has not been established. During therapy with Aggrastat, patients should be monitored for potential bleeding. When treatment of bleeding is required, discontinuation of the drug should be considered. Consideration may also be given to transfusions. Aggrastat is associated with minor increases in bleeding rates particularly at 'the site of arterial access for femoral sheath placement. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Care should be taken to obtain proper hemostasis after removal of the sheaths followed by close observation.

2.4.4b Precautions **(cont)**

b. Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 22 times the human dose and have revealed no harm to the fetus due to Aggrastat. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

c. Nursing Mothers

It is not known whether tirofiban is excreted in human milk. However, significant levels of Aggrastat were shown to be present in rat milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

d. 'Pediatrics

Safety and effectiveness in pediatric patients have not been established.

e. Geriatrics

Of the total number of patients in controlled clinical studies of Aggrastat, 42.8% were 65 years and over, while 11.7% were 75 and over. With respect to efficacy, the benefit of Aggrastat in the elderly (265 years) was comparable to that seen in younger patients (<65 years). Elderly patients receiving Aggrastat with heparin or heparin alone had a higher incidence of bleeding complications than younger patients. The incremental risk of bleeding in patients treated with Aggrastat in combination with heparin over the risk in patients treated with heparin alone was comparable regardless of age. The overall incidence of non-bleeding adverse events was higher in older patients (compared to younger patients); however, the incidence of non-bleeding adverse events in elderly patients receiving Aggrastat was comparable between the Aggrastat with heparin and the heparin alone groups. No dose adjustment is recommended in older populations.

f. Renal insufficiency

This drug is known to be excreted by the kidney. A 50% reduction in dose is recommended for patients with severe renal insufficiency (creatinine clearance <30 ml/min) (see dosage recommendations).

g. Carcinoeenesis. mutaeenesis. impairment of fertility

The carcinogenic potential of tirofiban has not been evaluated. Tirofiban was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and in vitro chromosomal aberration assays. Tirofiban was tested in these *in vitro* assays at concentrations up to 3 mM, approximately 20,000 times greater than the mean plasma level achieved in man at the recommended therapeutic dosage level. There was no induction of chromosomal aberrations in bone marrow cells of male mice after the administration of intravenous doses up to 5 mg/kg (22 times the maximum recommended daily human dose).

2.4.4c Proposed Monitoring

Platelet counts, and hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following the bolus or loading infusion, and at least daily thereafter during therapy with Aggrastat (or more frequently if there is evidence of significant decline). If the patient experiences a platelet decrease to <90,000 cells/mm^3, additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confinned, Aggrastat and heparin should be discontinued and the condition appropriately monitored and treated.

2.5 Foreign Marketing

As of 11.25.97, tirofiban has not received marketing approval in any country. Additionally, marketing approval of Tirofiban has not been withdrawn, rejected, or applied for, in any foreign country.

3.0 Chemistry, Manufacturing, and Controls

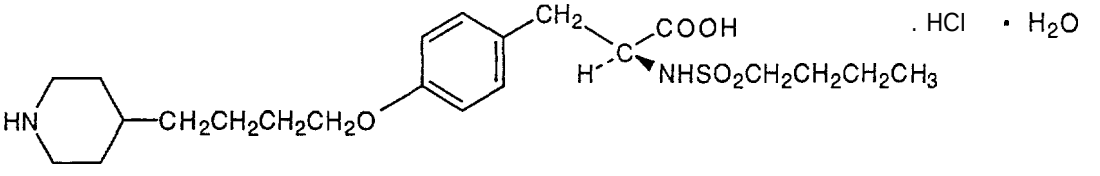
There are no known clinical implications of chemistry, manufacturing and control identified in consultation with the assigned manufacturing and control reviewer.

4.0 Pharmacology/ Pharmacokinetics

4.0.1 Pre-Clinical Pharmacology

Tirofiban hydrochloride monohydrate, a non-peptide molecule, is chemically described as N-(butylsulfonyl)-O-[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate. It is chemically unrelated to any approved or unapproved platelet antagonist, including Reopro and Integrilin.

Its empirical formula is $C_{22}H_{36}N_2O_5S*HCL*H_2O$ and its structural formula is:



The proposed clinical effects of tirofiban are related to its inhibition of fibrinogen binding to the platelet membrane protein, glycoprotein (GP) IIb/IIIa. This binding is an obligate step in the adhesion of platelets to disrupted vascular surfaces, which leads to the formation of thrombus. The effect of tirofiban to inhibit fibrinogen adhesion to platelets IIb/IIIa has been demonstrated in a variety of experimental systems (see NDA volume 1.2, Section F for details). The equilibrium dissociation constant for [^{3}H]-tirofiban from human platelets is 14 nM. There is also a dose-dependent inhibition of ADP-induced platelet activation *ex vivo* from dogs, and a dose of 10.0 µg/kg/min IV maintained near complete inhibition.

The use of tirofiban in combination with other anti-platelet agents has been explored in dogs. The combination of tirofiban, ASA and heparin resulted in a greater effect on bleeding times than any of the two agents alone (1.5 to 2.9-fold increase). When compared, heparin had a greater effect on bleeding times in combination with tirofiban than did enoxaparin. Tirofiban and ticlopidme together resulted in bleeding times that were greater than ticlopidine alone, and were slightly but not significantly greater than tirofiban alone.

The potential non-hematological effects of tirofiban were also examined in anesthetized and conscious dogs, and in conscious mice. No significant non-hematological effects of tirofiban were noted in the dogs. In mice, high doses of tirofiban (100 mg/kg intra-peritoneally) was sedating.

4.0.2 Pre-clinical Pharmacokinetics

The absorption, distribution, metabolism and excretion of tirofiban have been studied in rats and dogs. For details of the pre-clinical pharmacology the reader is referred to the Dr. Stolzenberg's review.

a. Absorption

In rats, the ratio between the amount of tirotiban in the urine following PO and IV administration was low, suggesting a limited oral absorption. Since the proposed use of tirotiban is intravenous, this is of limited clinical importance.

b. Distribution

When [^{3}H]- or [^{14}C]-labeled tirofiban was administered to rats and dogs, the majority of the radioactivity was recovered in the feces and bile. Radio-labeled tirofiban was synthesized using both [^{3}H] in the phenyl ring of the tyrosinyl residue or [^{14}C] in the butane sulfonyl moiety. When dogs received [^{3}H]-tirofiban, recoveries were approximately 83% in the feces and 9% in the urine by 72 hours. These results suggest that biliary excretion was the major route of elimination for tirofiban.

Following a single intravenous dose, the maximum concentrations ofradioactivity in blood and plasma were detected at 5 minutes, with values of 0.641 and 1.25 µg equivalents/gram respectively. These values decline rapidly so that by 24 hours the levels were below detectable levels. The maximum tissue concentrations also peaked after 5 minutes (with the exception of the GI track). The samples containing the highest percentage of the radioactive label at 5 minutes post-dose were the liver (49.3%), small intestine and contents (13.7%), skin (7.9%) and muscle (5.6%). After 30 minutes, the highest concentration of radioactivity was found in the small intestine contents (68.2%) liver (6.13%), and small intestine (4.5%). After 2 hours, the highest concentrations of radioactivity were found in the small intestine contents and wash (63.7%) the large intestine and wash (11.2%), and small intestine (4.94%). By 24 hours, less than 5% of the radioactivity remained in the body.

4.0.2 Pre-clinical Pharmacokinetics **(cont)**

c. Metabolism

The major urinary and biliary metabolite in rats was a molecule with a phenol formed through O-dealkylation, which represented 70% of the radioactivity in the urine and 30% of the bile radioactivity. In dogs, little metabolism was detected, and tirofiban was excreted mostly unchanged in the urine and feces.

Following incubation of radioactive tirofiban with rat and human liver microsomal preparations and human liver slices, a small percentage of the radioactivity in the rat was found to be present in a product formed through O-dealkylation of the parent compound. In humans, the radioactive isolates behaved chromatographically as the unchanged tirofiban parent compound, indicating no metabolite formation.

d. ***In Vitro*** Protein Binding

[^{3}H]-tirofiban was not highly bound to plasma proteins over the concentration range of 0.01 to 25 µg/ml. The binding was also species specific: unbound fractions in rat, monkey, human and dog plasma were 13-15%, 30-36%, 29-37%, and 50-57% respectively.

There was appreciable binding of [^{3}H]-tirofiban to unactivated platelets in humans. There was little association of [^{3}H]-tirofiban with RBCs in humans.

e. Excretion

The majority of the tirofiban was excreted unchanged in the urine and feces in both rats and dogs. When dogs received [^{3}H]-tirofiban, recoveries were approximately 83% in the feces and 9% in the urine by 72 hours.

f. Pharmacokinetics

Plasma concentrations of tirofiban declined rapidly after an IV bolus in both rats and dogs, as summarized in the table below. Over the dose range from 0.12 to 3.6 mg/kg IV, the plasma concentrations of tirofiban in dogs demonstrated linear kinetics (see NDA volume 1.19, Figure 7).

Table 4.0.2.1 Pharmacokinetic parameters of tirofiban in rats and dogs[a].

Species	Dose/Route	Clp (ml/min/kg)	Vd_{ss} (l/kg)	$t_{1/2}$ (min)
Rat (n=4)	5 mg/kg IV bolus	102±27	1.43±0.74	24±7
Dog (n=3)	0.12 mg/kg IV infusion	28±5	0.53±0.2	31±6
Dog (n=4)	1.2 mg/kg IV infusion	33±3	0.42±0.09	39±7
Dog (n=4)	3.5 mg/kg IV infusion	28±2	0.35±0.05	35±5

a. Data from NDA volume 1.2, Table G-3, and volume 1.19, sections G-1 and G-2.

4.1 Toxicology/ **Genotoxicity/ Carcinogenicity**

The potential toxicity of tirofiban was studied *in vivo* and *in vitro,* including: single-dose studies in rats and mice; repeated-dose studies in rats and dogs (up to 5 weeks); genetic toxicity studies; and developmental and reproductive toxicity studies in rats and rabbits.

a. Single-dose Studies

Acute intravenous doses of tirofiban up to 5 mg/kg, or oral doses up to 500 mg/kg caused no mortality, clinical signs, or effect on body weight in either rats or mice, suggesting that tirofiban has a low order of acute toxicity in these species. The maximum IV dose was limited by compound stability and solubility in acceptable dosing volumes.

b. Repeated-dose Studies

Repeated-dose studies for up to 5 weeks were performed in rats and dogs using the intravenous formulation. The dogs received either boluses for 6 hours or continuous infusion at dosage rates of 1, 10, and 30 µg/kg/min. In the rats, no excess mortality, changes in organ weight or gross or microscopic pathologic changes were detected.

In dogs, hemorrhage and testicular degeneration were noted at the 30 µg/kg/min dose.

The hemorrhage noted was limited to focal hemorrhage in the spleen and retina (one dog each) or venipuncture site (one dog). Platelets from dogs at the two highest doses (10 and 30 µg/kg/min) exhibited complete inhibition of platelet aggregation when tested *ex vivo.* Platelet function returned to normal within 24 hours of stopping the tirofiban in all dogs.

4.1 Toxicology/ **Genotoxicity/** Carcinogenicity

b. Repeated-dose Studies **(cont)**

Testicular degeneration was noted in the 2/4 dogs at the 10 µg/kg/min dose, and 214 dogs at the 30 µg/kg/min dogs in the 5 week trial. No similar effect of tirofiban was noted in two other studies lasting 18 days and 16 days, which included a dose of 30 µg/kg/min. The sponsor estimated a no-effect dose of 1 µg/kg/min, which represents a 45-fold excess over the recommended human dose. Since the effect appeared to the time-dependent, the sponsor also calculated the dose based on a 2 week infusion. Under that circumstance, the dog-dose at 1 µg/kg/min is 690 times the upper limit for recommended human use.

c. **Genotoxicity/Mutagenicity**

Tirofiban hydrochloride was negative in multiple microbial mutagenesis assays utilizing two different bacterial species *(Salmonella* and *E. coli)* up to the maximum testable dose (limited by compound solubility) with and without metabolic (S-9) activation. Tirofiban hydrochloride was also negative in duplicate mammalian cell (V-79, Chinese hamster lung cell system) mutagenesis assays up to the maximum doses tested (3.0 mM, limited by compound solubility and/or cytotoxicity) with and without metabolic activation.

Tirofiban was negative in a test of DNA strand breakage, the *in vitro* alkaline elution/rat hepatocyte assay, at concentrations up to 1.0 mM, a concentration limited by compound solubility. Tirofiban was also negative in the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at concentrations up to 1.75 mM, a concentration limited by compound solubility. Tirofiban was also tested in male mice for its potential to induce chromosomal aberrations in bone marrow cells at intravenous dosages of 1, 2 and 5 mg/kg. The top dose was chosen based on compound solubility and maximum acceptable intravenous dosing volume in mice (12.5 ml/kg). Tirofiban hydrochloride was negative in the chromosomal aberration assay in bone marrow of male mice under the conditions of the assay. In summary, tirofiban hydrochloride did not display mutagenic or genotoxic potential in a series of in *vitro* assays and in an in *vivo* assay for chromosomal aberrations in mouse bone marrow.

d. Reproductive Toxicity

A series of studies was performed in rats and rabbits to evaluate the potential reproductive and developmental toxicity oftirofiban. Additionally, the presence of tirofiban hydrochloride was documented in blood of fetal rats and rabbits after maternal exposure and in the milk of lactating rats. The top dosage used in these studies (5 mg/kg/day) was limited by compound solubility and acceptable dosing volumes for bolus intravenous administration. The effect of tirofiban hydrochloride on fertility in male rats was evaluated by administering 1, 2, or 5 mg/kg/day IV for 15 and 29 days prior to cohabitation (two periods of cohabitation employed) with untreated females. Treatment of males was continued during and after cohabitation for a total of approximately seven weeks. Evaluation at termination included enumeration of sperm in the cauda epididymis, evaluation of motility of sperm collected from the vas deferens, recording of testicular weights, and morphologic examination of testes and epididymides. There were no treatment-related effects on male reproductive parameters. Potential effects of tirofiban hydrochloride on fertility of female rats were evaluated by administering 1, 2, or 5 mg/kg/day of tirofiban by intravenous injection beginning 14 days prior to cohabitation with untreated male rats and continuing treatment through gestation day 7. Fertility indices evaluated included time to mating, percentage of females that mated, fecundity index, preirnplantation loss, percent resorptions plus dead fetuses and average numbers of implants and live fetuses per pregnant female. There were no treatment-related effects on female fertility.

In rats, two developmental toxicity studies were performed. In one study, developmental toxicity during the prenatal period was evaluated by administering 1, 2 or 5 mg/kg/day of tirofiban hydrochloride to pregnant females from gestation days 6 through 20. When fetuses were examined on gestation day 21, no effects of tirofiban were observed.

In another developmental toxicity study in rats, the potential developmental toxicity through sexual maturity of animals exposed *in utero* and during lactation was evaluated by administering 1, 2, or 5 mg/kg/day of tirofiban hydrochloride by intravenous injection to females from Day 6 of gestation through Day 20 of lactation. The F-l generation was evaluated through postnatal week 17. There were no drug-related effects on mortality, growth, development, and sexual maturation of the F- 1 generation.

In a separate study, maternal and fetal plasma concentrations of tirofiban hydrochloride on gestation day 20 and maternal plasma and milk concentrations on lactation Day 14 were measured. The results of this study indicated that fetuses and pups were exposed to tirofiban hydrochloride in blood and milk, respectively.

4.1 Toxicology/ Genotoxicity/ Carcinogenicity

d. Reproductive Toxicity (cont)

The potential effects of tirofiban hydrochloride on development in rabbits were evaluated by administering 1, 2, or 5 mg/kg/day of tirofiban hydrochloride by intravenous injection to pregnant rabbits from gestation day 7 through 20 of gestation. When fetuses were examined on gestation day 28, there was no evidence of maternal or fetal toxicity. In a separate study, evaluation of maternal and fetal plasma concentrations of tirofiban hydrochloride on gestation day 20 indicated that significant fetal exposure to tirofiban hydrochloride was achieved.

In summary, tirofiban was evaluated in rats and rabbits for its potential to cause developmental and reproductive toxicity. No evidence of reproductive or developmental toxicity was observed in these studies, and there is no contraindication for exposing women of child-bearing potential to tirofiban hydrochloride. Tirofiban does enter the milk in rats in detectable quantities.

5.0 Description of Clinical Data Sources

The data source for this primary medical and statistical review of NDA 20-912 comes from the computer-assisted New Drug Application (CANDA) submitted by the sponsor containing the entire NDA, along with the paper submission consisting of 90 volumes. These sources were discussed in section 1.1 above.

In addition, the sponsor submitted data not included in the NDA for several aspects of efficacy or safety, at the request of the primary medical or statistical reviewer. These materials are identified as to their source where appropriate.

5.1 Primary Source Data (Development Program)

5.1.1 Study Type and Design/Patient Enumeration

The tirofiban development program consisted of 12 clinical studies: 6 pharmacokinetic/pharmacodynamic studies of Tirofiban alone and in combination with ASA; 3 small Phase II dose-ranging studies of tirofiban alone and in the presence of heparin and ASA; and 3 phase III trials of tirofiban alone and/or in the presence of ASA and heparin. The three Phase III studies are double-blind, active-controlled trials, with a total of 7288 randomized subjects, and form the basis for the sponsor's claim of efficacy of tirofiban in reducing ischemic cardiac events in subjects at risk.

Table 5.1.1.1 Overview of tirofiban clinical development program[a].

Protocol	Study Population	# of Subjects	Study Drug(s)	Control Group
Clinical Pharmacology Studies				
#001	Healthy Subjects	44	Tirofiban	Placebo
#002	Healthy Subjects	12	Tirotiban ± ASA	Placebo
#004	Stable CAD[b,e]	24	Tirotiban ± ASA	Placebo
#009	Hepatic Insufficiency	24	Tirofiban	Subjects with CAC Placebo Healthy Subjects
#012	Healthy Subjects	6	^{14}C-Tirofiban	None
#014	Renal Insufficiency	31	Tirofiban	Placebo Healthy Subjects
Phase II Dose-Ranging Studies[e]				
#005	UAP/NQWMI[c]	102	Tirofiban	Heparin
#007	ACS for PTCA[d]	93	Tirotiban +Heparin	Placebo
#008	UAP/NQWMI	48	Tirofiban +Heparin	Heparin
Phase III Clinical Efficacy & Safety Studies[e]				
#006 (PRISM-PLUS)	UAP/NQWMI	1915	Tirofiban +Heparin Tirofiban	Heparin
#011 (PRISM)	UAPMQWMI	3232	Tirotiban	Heparin
#013 (RESTORE)	ACS for PTCA	2141	Tirotiban (+Heparin)[f]	Placebo (+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 also received ASA unless contraindicated for the individual subject
f. All subjects in the RESTORE trial received heparin, in addition to tirofiban or placebo.

51.2 Demographics

The next section compares the demographics of the phase III trials. First, the demographics of the three treatment groups are compared. Overall, the demographics were well-balanced.

Table 5.1.2.1 Combined Demographics of the Phase II-III tri[a].

Demographic	Tirofiban (n=2032)	Tirofiban +Heparin (n=1953)	Heparin (n=3546)	Total (n=7531)
Gender				
Female	664 (32.7%)	569 (29.1%)	1058 (29.8%)	2291 (30.4%)
Male	1368 (67.3%)	1384 (70.9%)	2488 (72.2%)	5240 (69.6%)
Race				
White	1727 (85.0%)	1693 (86.7%)	3049 (86.0%)	6469 (85.9%)
Black	98 (4.8%)	117 (6.0%)	154 (4.3%)	369 (4.9%)
Asian	32 (1.6%)	10 (0.5%)	58 (1.6%)	100 (1.3%)
Hispanic	98 (4.8%)	88 (4.5%)	167 (4.7%)	353 (4.7%)
Other	77 (3.8%)	45 (2.3%)	118 (3.3%)	240 (3.2%)
Age (years)				
o-34	7 (0.3%)	19 (1.0%)	18 (0.8%)	44 (0.6%)
34-44	106 (5.2%)	169 (8.7%)	241 (6.8%)	516 (6.9%)
45-54	394 (19.4%)	429 (22.0%)	738 (20.8%)	1561 (20.7%)
55-65	586 (28.8%)	557 (28.5%)	1045 (29.5%)	2188 (29.1%)
65-74	636 (31.3%)	550 (28.2%)	1063 (30.0%)	2249 (29.9%)
75-99	303 (14.9%)	229 (11.7%)	441 (12.4%)	973 (12.9%)
Mean age±sd	62.7±11.1	60.5±11.5	61.5f11.3	61.6±11.3
Median age	63.0	61.0	62.0	62.0
Range	27-93	22-94	20-93	20-94
Weight (kg)				
o-74	871 (42.9%)	707 (36.2%)	1334 (37.6%)	2912 (38.7%)
75-85	590 (29.0%)	572 (29.3%)	1043 (29.4%)	2205 (29.3%)
≥86	568 (28.0%)	674 (34.5%)	1167 (32.9%)	2409 (32.0%)
Missing	3 (0.1%)	0 (0 %)	2 (0.1%)	5 (0.1%)
Mean weight ±sd	78.1±15.6	81.2f18.0	80.1f16.3	79.8±16.7
Median weight	77.0	80.0	79.0	78.0
Range	35-173	33-228	35-196	33-228

a. From NDA volume 1.69, re ence 247. Includes protocols 005, 006, 00 08, 011 and 013.

5.1.2 Demographics

The next table summarizes the demographics of the three phase III trials. The demographics of the treatment groups within each trial are to be found in the individual study reviews.

Table 5.1.2.2 Individual demographics of the PRISM-PLUS, PRISM, and RESTORE tria

Demographic	PRISM-PLUS (n=1915)	PRISM (n=3232)	RESTORE (n=2141)
Gender			
Female	620 (32.4%)	1034 (32.0%)	582 (27.2%)
Male	1295 (67.6%)	2198 (68%)	1559 (73%)
Race			
White	1651 (86%)	2703 (83.6%)	1905 (89.0%)
Black	73 (3.8%)	158 (4.9%)	120 (5.6%)
Asian	14 (0.7%)	70 (2.2%)	16 (0.7%)
Hispanic	97 (5.1%)	170 (5.3%)	75 (3.5%)
Other	80 (4.2%)	131 (4.1%)	25 (1.2%)
Common Diagnosis			
Hypertension	1047 (54.7%)	1758 (54.4%)	1173 (54.8%)
Hypercholesterolemia	948 (49/5%)	1532 (47.4%)	1062 (49.6%)
Family Hx of heart disease	909 (47.5%)	1317 (40.7%)	1117 (52.2%)
Hx of MI	810 (42.3%)	1517 (46.9%)	745 (34.8%)
Diabetes	447 (23.3%)	687 (21.2%)	420 (19.6%)
Age (mean±sd)	63.2±11.6	62.4±11.1	59.0±11.0
Range	26 to 94	20 to 93	25 to 85
Weight (kg) (Males)	80.3±14.1	82.0±14.9	87.6±15.3
Weight (kg) (Females)	68.7±14.1	71.7±15.5	73.3±16.5

a. From NDA volume 1.2, section 4.2.

5.1.3 Extent of Exposure (dose/duration)

Tirofiban was administered using several protocols as part of the drug development program, as summarized below. A further discussion of the choice of tirofiban and heparin dosing in the phase III trials is found in appendix 8, section 20.0. First, the number of subjects in each of the tirofiban regimens is summarized.

Table 5.1.3.1 Number of subjects randomized to phase II and III studies, grouped according to the tirofiban regimen use[a].

Tirofiban regimen	Without Heparin		With Heparin	
	Protocol #	# of Subjects	Protocol #	# of Subjects
1. Loading: 0.3 µg/kg/min x 30 mins Maintenance: 0.075 µg/kg/min	005	28		0
2. Loading: 0.4 µg/kg/min x 30 mins Maintenance: 0.1 µg/kg/min	005	23	008 006 (PRISM-PLUS)	794
3. Loading: 0.6 µg/kg/min x 30 mins Maintenance: 0.15 µg/kg/min	005 006 (PRISM-PLUS) 011 (PRISM)	1981	008	15
4. Bolus:5 µg/kg/min x 5 mins Maintenance: 0.05 µg/kg/min		0	007	21
5. Bolus: 10 µg/kg/min x 5 mins Maintenance: 0.1 µg/kg/min		0	007	30
6. Bolus: 10 µg/kg/min x 3 to 5 mins Maintenance: 0.15 µg/kg/min		0	007 013 (RESTORE)	1144

a. Data from NDA volume 1.2, table C-32 and C-33

5.1.3 Extent of Exposure (dose/duration) **(cont)**

Next, the number of subjects in each study is grouped according to study drug administration.

Table 5.1.3.2 Number of subjects in the Phase II-III trials, grouped according the study drug(s) administered".

Protocol	# of Tirofiban Subjects	# of Tirofiban + Heparin Subjects	# of Heparin Subjects
Phase II Dose-Ranging Studies			
#005	71		31
#008		36	12
#007		73	20
Phase III Clinical Efficacy & Safety Studies			
#006 (PRISM-PLUS)	345	773	797
#011 (PRISM)	1616		1616
#013 (RESTORE)		1071	1070
Total	2032	1953	3546
Corrected Total[b]	2002	1946	3546

a. Data from NDA volume 1.37

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).

Tirofiban Dose

The cumulative tirofiban dose of exposure is summarized in the table below.

Table .3.3 Cumulative rofiban dose posure for the subjects in the Phase II-III trials".

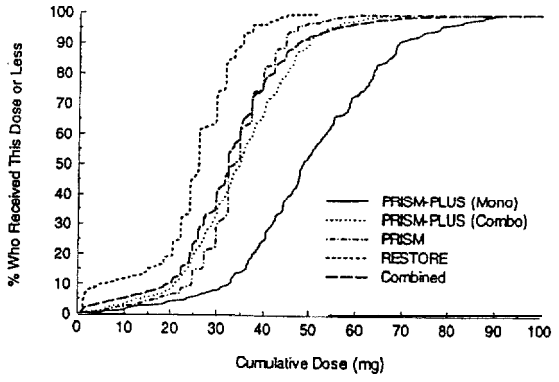
Cumulative Dose (mgs)	Tirofiban Alone (n=2002)	Tirofiban +Heparin (n-1946)	**Heparin Alone (n=3948)**
>0 to <5	18	125	143
≥5 to **<10**	32	67	99
210 to **<15**	46	80	126
≥15 to **<20**	59	81	140
≥20 to **<25**	142	377	519
≥25 to **<30**	268	426	694
230 to **<35**	530	310	840
≥35 to **<40**	365	200	565
≥40 to **<45**	236	132	368
245 to **<50**	101	83	184
≤50 to 155	63	31	94
≥55 to **<60**	45	19	64
260 to **<65**	39	11	550
≥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 **≤90**	5	0	5
290 to **<95**	1	0	1
295 to **<100**	0	0	0
≥100 to **≤105**	0	0	0
≥105 to **≤110**	0	1	0

a. Data from NDA v me 1.2, table C 4, for those randomized subjects who received at least one dose of study drug.

51.3 Extent of Exposure (dose/duration) (cont)

The majority of subjects exposed to tirofiban were in the three phase III trials. The figure below shows the cumulative dose of tirofiban in each of the three trials. Note that the subjects in the RESTORE trial received significantly less total tirofiban on average.

Figure 5. I .3.1 Distribution function for cumulative dose of tirofiban for all subjects in the PRISM-PLUS, PRISM, and RESTORE trials.



Next, the cumulative time of exposure to tirofiban from the phase II-III trials is summarized in the table below.

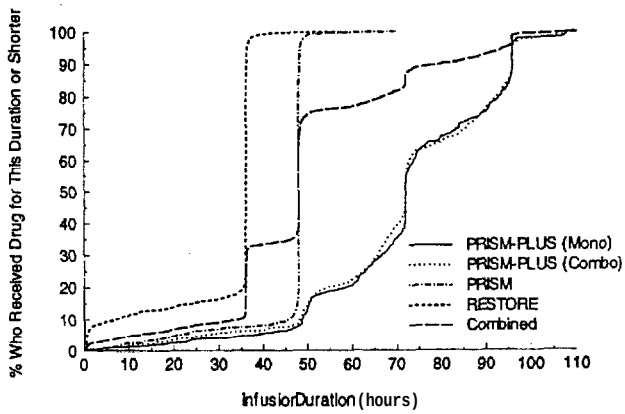
Table 1.3.5 Cumulative time of tirofiban exposure for the subjects in the Phase II-III trials.

Cumulative Dose (mgs)	Tirofiban (n=2002)	Placebo/ Heparin (n=1946)	Combined (n=3948)
* 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
255 to <60	8	18	26
260 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
285 to 590	11	48	59
≥90 to <95	28	61	89
≥95 to <100	51	104	155
≥100 to <105	0	5	5
1105 to <110	6	10	16
1110 to <115	0	3	3
1115 to <120	1	0	1

5.1.3 Extent of Exposure {dose/duration) **(cont)**

The majority of subjects exposed to tirofiban were in the three phase III trials. The figure below shows the cumulative duration of exposure to tirofiban in the phase III trials. The total dose of tirofiban administered, as well as the duration of tirofiban infusion, varied between the three phase III protocols. Overall, the subjects in the RESTORE trial received a lower total dose of tirofiban for a shorter period of time than the subjects in the PRISM and PRISM-PLUS trials. Subjects in the PRISM-PLUS trial received tirofiban for an average of 72 hours (see table 6.2.1.12.2c.2). Subjects in the PRISM trial received tirofiban for an average of 46 hours (see table 6.2.2.12.2c.2). Subjects in the RESTORE trial received tirofiban for an average of 30 hours (see table 6.2.3.12.2.3).

Figure 5.1.3.2 Distribution function for duration of exposure to tirofiban for all subjects in the PRISM-PLUS, PRISM, and RESTORE trials.



Heparin Dose

The amount of heparin administered varied between studies, with RESTORE subjects getting a lower dose of heparin on average. In the PRISM-PLUS trial, heparin was administered at a total dose of approximately 80,000 Units (U) of heparin (see table 6.2.1.12.2c.3). In the PRISM trial, information regarding total heparin dose is not available (heparin was only administered in one of the two arms). In the RESTORE trial, subjects received an average of 11,000 U of heparin (see table 6.2.3.12.2.1).

The duration of heparin administration varied between the three trials, again with subjects in the RESTORE receiving heparin for a shorter average amount of time. In the PRISM-PLUS trial, heparin was administered for an average of over 70 hours (see table 6.2.1.12.2c.2). In the PRISM trial, subjects received heparin for an average of 45.9 hours (see table 6.2.2.12.2c.2). In the RESTORE trial, subjects received heparin for an average of approximately 20 hours (see table 6.2.3.12.2. 1).

5.2 Secondary Source Data

No secondary data sources were used in this NDA review.

5.2.1 Other Studies

No studies on the clinical use of tirofiban, other than those included in the NDA, were available for consideration.

5.2.2 Post-Marketing Experience

Tirofiban has not been previously marketed.

5.2.3 Literature

Two approaches were used to identify relevant published literature relevant to the current submission,

First, an independent literature review, through a keyword search of Medline, was conducted by this reviewer. Terms used in the search included: angina pectoris; angioplasty; human clinical trials.

Second, the sponsor has provided a literature review, which was cross-referenced with the above reviews to assure completeness. The cut-off for consideration of articles in this NDA was approximately June of 1997. This literature review has been incorporated into the background section of this introduction, and into the integrated safety summary, where a comparison of the safety adverse events for the various IIb/IIIa receptor antagonists is performed.

5.3 Comment on Adequacy of Clinical Experience

The database for NDA 20-912 contains a total of 3985 subjects randomized to receive tirofiban as part of a phase II-III trial, along with 3546 subjects randomized to receive heparin. The overall demographics of this trial population were reviewed above. Over all, enough subjects in various demographic subgroups were enrolled to allow some reasonable inferences to be made concerning the effect of tirofiban related to gender, age, and race.

The trial also includes subjects who received a relatively broad range of doses for varying intervals of time. Tirofiban is proposed for use for a relatively short interval following the onset of acute coronary syndrome (maximum duration, 108 hours).

It is also worthwhile noting that the phase III trials each contained important exclusion criteria which limit the general applicability of the results to subjects with co-existing medical conditions. The details of these exclusions are reviewed in the relevant sections of each trial,. but the all three trials excluded subjects with clinically important systemic, renal (creatinine X.0-2.5 mg/dl), pulmonary, hepatic, endocrine (e.g., uncontrolled diabetes or uncontrolled thyroid disease), neurological, or hematological disorders. Subjects with recent (6 months) coronary angioplasty were also excluded from consideration.

The phase III trials also limited enrollment to subjects with recent onset of UAP/NQWMI symptoms (72 hours in RESTORE, 12 hours in PRISM-PLUS, 24 hours in PRISM). Subjects who had their last angina1 symptoms further in the past were not eligible for enrollment.

The database also includes relatively few subjects in certain sub-groups. Most relevant are the small number of non-white subjects in the database (Black 369; Asian, 100; Hispanic 353; Other 240), and the small number of subjects with renal and hepatic disease, who were excluded per-protocol from the phase III trials.

Finally, the number of subjects in the database puts limits on the ability to detect adverse events. A database with the stated size has the power to detect a single occurrence of AEs occurring at a rate of approximately one per 2500 subjects with 95% confidence. The ability to make inferences concerning relative rates is obviously much more limited given the size of the database.

With these qualifications, the tirotiban database includes a sufficient number of subjects to adequately assess both the safety and efficacy of tirofiban in this population.

5.4 Comment on Data Quality and Completeness

Specifics regarding the completeness of the database for NDA 20-9 12 will be made during each trial review. Overall, follow-up for subjects was adequate for the primary endpoint and its components in each of the phase III trials. Follow-up for abnormal laboratories was dependent on the individual investigators, and the submitted lab data did not include some analyses of interest. At the request of the reviewers, however, the sponsor performed additional analyses which added materially to the database. Where identified, all discrepancies have been succesfully resolved between the sponsor and the reviewers. The FDA has not yet validated the determination of clinical events performed by the Endpoints Committees, as well as most of the safety analyses performed by the sponsor.

In summary, the data quality and completeness is acceptable for a medical and statistical review. Specific problems regarding the adequacy of the data are noted as well at appropriate points in the review document.

6.0 Review of Individual Studies

The following six sections review the trials that make up the phase II-III database. This database contains a' total of 7531 subjects randomized to receive one of the following three therapies as part of the 6 trials: 2032 in the tirofiban alone group; 1953 in the tirofiban +heparin group; and 3546 in the heparin alone group.

The first three reviews will be of phase II trials designed to investigate the pharmacokinetics and pharmacodynamics of tirofiban. Based on these trials (as well as earlier, phase I-II trials reviewed by Dr. Pelayo separately), the three pivotal phase III trials were performed: PRISM-PLUS; PRISM; and RESTORE.

Each trial will be reviewed, in a standard format, beginning with a review of the background and proposed design of each trial. This will be followed by a review of the baseline characteristics of the subjects in each trial, including demographics and concomitant medications. Next, the results of each trial will be reviewed; first efficacy, and then safety. Following this, each review will have an integrated efficacy and safety summary of the trial results. Following a review of the three pivotal phase III trials (sections 6.2.1, 6.2.2 and 6.2.3), an integrated efficacy summary of all of the phase II-III trials will be performed.

6.1.1 Review of Protocol #005

6.1.1.1 Title of Study

A Randomized, Double-Blind, Heparin-Controlled, Dose-Finding Study of Tirofiban in Subjects With Unstable Angina Pectoris (Protocol #005).

6.1.2 Sites of Investigation and Investigators

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

Protocol #005 was conducted by 11 investigators in Europe, Canada, Australia, Israel, and New Zealand.

6.1.1.3 Background

Initial Protocol: submitted 12.9.92

First protocol amendment: submitted 9.1.93

1. Expanded the sample size from 60 to 90 subjects by adding on a third panel to the study design, which received a higher dose of tirofiban.

Subject entry: 3.93 through 12.93

Case report form cutoff: 1.3 1.94

6.1.1.4 Study Design

This was a randomized, double-blind, heparin-controlled, multicenter, multinational study in subjects with unstable angina pectoris/ non-Q-wave MI (UAP/NQWMI). Thirty subjects in three panels were studied sequentially, with 20 subjects receiving MK-0383 (tirofiban) and 10 subjects receiving heparin.

Baseline period

After hospital admission, potential subjects underwent a medical history review and a physical examination. Additionally, each subject had a 12-lead electrocardiogram (ECG), CXR, complete laboratory evaluation including stool for occult blood, prothrombin time (PT), activated partial thromboplastin time (aPTT) and creatine lcmase (CPK), with isoenzymes if available. Subjects were excluded from the study if they had received an oral anticoagulant medication (i.e., warfarin) 1 week prior to study start. Antiplatelet agents, such as dipyridamole, sulfinpyrazone and nonsteroidal anti-inflammatory agents, must not have been ingested within 24 hours prior to enrollment; subjects receiving ticlopidine within 7 days of study enrollment were not eligible for enrollment. Medications other than antiplatelet/ anticoagulant drugs were prescribed during hospitalization at the discretion of the physician. 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.

Double-blind treatment period, hours 0 to 48

After completion of the baseline evaluations, eligible subjects were randomized to receive tirofiban or heparin. Following venous access, the subject received study drug bolus, followed by an infusion. Study drug was to be initiated within 48 hours following the last episode of chest pain. At hours 6 and 24 (and as needed), an unblinded coinvestigator monitored the aPTT and adjusted the heparin infusion to maintain aPTT approximately 1.5 to 2X control using a nomogram provided by the sponsor. In subjects receiving tirofiban, there was also a random adjustment of the placebo for heparin; and the unblinded investigator received prespecified instructions on adjustment of this "dummy" (D5W) infusion. Study drug was infused for 48 hours, when a complete laboratory and physical examination was performed. The subject remained under close supervision an additional 24 hours or until clinically stable, after which time the IV could be removed. Subjects were monitored for both pharmacokinetic and clinical events during the trial, as detailed below.

6.1.1.5 Primary and Secondary Endpoints

The primary aim of the study was to collect pharrnacokinetic and pharmacodynamic data, including:

1) Serial tirofiban serum concentrations;
2) Serial measurements of the % inhibition of ADP-induced platelet aggregation (IPA); and
3) Serial measurements of the extension of bleeding times (BTE).

While not powered to detect differences in clinical endpoints, the study did collect information about the following clinical events:

1) Ischemic episodes;
2) Refractory angina pectoris;
3) Myocardial infarction; and
4) Need for revascularization.

6.1.1.6 Number of subjects/ randomization

Table 6.1.1.6.1 Subjects enrolled in protocol #005.

Tirofiban regimen [b]			Heparin
Tirofiban 0.3/0.075 n=28	Tirofiban 0.4/0.1[c] n=23	Tirofiban 0.6/0.15 n=20	n=31

a. Data from NDA volume 1.40, Reference 4, Table 3.
b. Tirofiban groups shown as amount of bolus/ rate of infusion (in µg/kg/min).
c. During this review, the first number stands for the bolus, in µg/kg/min for 30 minutes, and the second number for the infusion, in µg/kg/min over the remainder of the infusion period.

6.1.1.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

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

1) Accelerating pattern of anginal pain (episodes of angina that were more frequent, severe, longer in duration and/or precipitated by less exertion) with electrocardiographic evidence of myocardial ischemia, defined as follows:
   a) persistent or transient ST-segment depression 20.1 mV (0.08 seconds after the J-point) in two contiguous leads; or
   b) persistent or transient T-wave inversion in two contiguous leads; or
   c) transient (<20 min) ST-segment elevation 10.1 mV in two contiguous leads.
2) Recent onset of chest pain (<4 weeks) which was suggestive of myocardial ischemia, 25 minutes but not longer than 1 hour in duration, and occurring at rest or with minimal effort;
3) Angina pectoris occurring at rest, or frequently (≥2 episodes/day) with modest activity, during the 2 weeks prior to study enrollment. It was expected that a certain number of subjects who presented with chest pain and ST-segment deviation of T-wave inversion would have creatine kinase (CPK) elevations consistent with a non-Q-wave myocardial infarction. Evidence of a non-Q-wave infarction did not exclude the subject from the study.

Subjects must:

1) Have had their most recent episode of chest pain within 48 hours preceding the time of randomization.
2) Have clinical evidence of underlying coronary artery disease by having one of the following:
   a) Electrocardiographic evidence of myocardial ischemia during an episode of chest pain.
   b) Prior history of myocardial infarction, positive exercise stress test or dipyridamole (or adenosine) nuclear stress test, or ≥50% luminal diameter narrowing of a major coronary artery on a prior coronary arteriogram.
   c) Typical exertional chest pain relieved by rest or nitroglycerin, or both.
3) Be ≥18 and ≤80 years of age.

Exclusion Criteria

1) Pregnant or nursing women and women of childbearing potential.

2) Presence of new pathologic Q-waves (>0.03 sec in duration) or ST-segment elevation ≥0.1 mV in two contiguous leads persisting for ≥20 minutes, suggestive of evolving acute Q-wave myocardial infarction.

3) Coronary angioplasty within 6 months or coronary bypass surgery within 3 months.

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

5) Subjects with uncontrolled severe cardiac arrhythmias, incldubg persistent sinus tachycardia >120 BPM.

6) Subjects receiving oral anticoagulant medications (i.e., warfarin) within 1 week prior to enrollment or antiplatelet agents (except aspirin) which have been ingested within 24 hours of enrollment (such as nonsteroidal anti-inflammatory agents, dipyridamole, and sulfinpyrazone). Subjects receiving ticlopidine within 7 days of study enrollment were not eligible for randomization.

7) a) Heparin allergy or intolerance (including heparin-induced thrombocytopenia).

b) Aspirin allergy or intolerance.

8) Thrombolytic therapy within 3 weeks prior to enrollment, or documented myocardial infarction within 3 weeks prior to the most recent episode of chest pain.

9) Contraindications to anticoagulation:

a) Past or present bleeding disorder including a history of gastrointestinal bleeding or presence of occult blood in the stool. Any subject with a known platelet disorder, history of thrombocytopenia or previous exposure to fibrinogen receptor antagonist were also 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 cerebrovascular disease including transient ischemic attacks.

d) Prolonged cardiopulmonary resuscitation with 1 minute or more of external cardiac massage within the 2 weeks prior to study enrollment.

e) Severe trauma within 6 months prior to study enrollment.

f) Major surgical procedure within 3 months of study enrollment.

g) Active peptic ulcer disease within 6 months prior to study enrollment.

h) Invasive procedure (or lithotripsy) within 14 days of study enrollment that would significantly increase the risk of hemorrhage, such as biopsy, or arterial puncture.

i) Probable pericarditis.

j) Presence of significant retinopathy (i.e., hemorrhages or exudates).

10) Angina precipitated by obvious provoking factors (e.g., arrhythmia, severe anemia, hypotension, or hyperthyroidism).

11) Left bundle branch block.

12) Pre-excitation syndrome, e.g., Wolff-Parkinson-White syndrome.

13) History of recent or ongoing alcohol abuse, or parenteral or other drug abuse,

14) 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).

15) Subjects with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.

16) Subjects with uncontrolled diabetes mellitus or other uncontrolled endocrinopathy.

17) Subjects with significant systemic, renal, pulmonary, hepatic, neurological or hematological disorders.

IS) Subjects with clinically significant abnormal laboratory findings including:

a) Serum creatinine >1.6 mg/dL (>140 μmol/L).

b) Hemoglobin <12 gm/dL (120 g/L) or hematocrit <36%.

c) Platelet count <150,000/mm^3 (<150 x 10^9 /L).

d) Prothrombin time or activated partial thromboplastin time (APTT) >1.2 x laboratory control.

19) Sustained supine, sitting or standing systolic blood pressure <90 mmHg.

20) Subjects receiving another investigational drug within 4 weeks prior to the study.

21) Subjects with any other medical condition, that, in the investigator's opinion, makes 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.

22) Inability to give informed consent.

6.1.1.8 Dosage/ Administration

In subjects previously treated with aspirin, 325 mg of aspirin was administered within 12 hours prior to initiation of study drug and after 24 hours of the study. In subjects not previously treated with ASA, 325 mg was administered after 36 hours. After 48 hours, the subsequent daily dosage of aspirin was at the investigator's discretion.

6.1.1.9 Duration/ Adjustment of Therapy

Subjects received either heparin or tirofiban for a total of 48 hours. 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, administration of the study drug was to be stopped. Such events included clinically relevant hemorrhage, or a significant decrease (>3g/dL) in blood hemoglobin from pre-drug values. The study drug was also to be discontinued for any persistent platelet count less than $90{,}000/mm^3$. Subjects were also to be discontinued from the study for the following: 1) A condition that necessitates thrombolytic therapy. 2) Must undergo emergent angiography or revascularization. 3) Need for intra-aortic balloon counter-pulsation.

In the event the infusion was discontinued prematurely, blood samples were to be obtained for measurement of AD&induced platelet aggregation and plasma tirofiban. Urine collection was to be terminated. The subject was to void completely and the urine collected up to that point was to be sent for measurement of urine creatinine. A complete laboratory screen was to be performed. A bleeding time was to be determined (if the subject was discontinued prior to hour 24). The subject was to be monitored for at least 24 hours after study drug had been discontinued and, if possible, post-drug evaluations normally performed at hour 60 were to be performed 12 hours after drug cessation.

6.1.1.10 Safety and Efficacy Endpoints Measured

The table below summarizes the efficacy and safety measurements performed during the trial, along with their time of measurement.

Table 6.1.1.10.1 Timetable for clinical observations and lab measurements in protocol #005[a].

	0 hrs Start of infusion	0.5 hrs	2 hrs	6 hrs	12 hrs	24 hrs	36 hrs	48 hrs Stop Infusion	60 hrs
History	X								
Physical exam	X					X		X	
CXR	X								
ECG	X				X	X		X	
Plasma tirofiban level	X	X				X	X	X	X
ADP-induced platelet aggregation	X	X				X	X	X	X
Bleeding Time	X					X		X	
PT/aPTT	X			X		X		X	X
Lab work[b]	X					X		X	
Hemoglobin/Hct	X	X	X	X	X	X	X	X	X
Platelet count	X	X	X	X	X	X	X	X	X
Urine for tirofiban	X					X			
	X								
ASA	X							X	
Study Drug									
Adverse event /endpoints									

a. Data from NDA volume 1.40, reference 4, table 1.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis) and (4) Stool for occult blood (as available).

6.1.1.11 Statistical Considerations

b) Efficacy

The primary hypothesis was that tirofiban would be safe and well-tolerated when administer in subjects with UAP/NQWMI receiving the doses detailed above. The sponsor proposed that if none of the 20 subjects in a given dose group (panel) suffered a clinical event, such as thrombocytopenia or bleeding, that there was an 80% confidence that the true rate for that adverse event was ≤8%.

The second hypothesis was that tirofiban would inhibit ADP-induced platelet aggregation (IPA) in a dose-dependent manner in subjects with UAP/NQWMI. The sponsor calculated that with 20 subjects per panel, and assuming a standard deviation of 16%, there was an 80% likelihood of being able to detect an increase of 15% between two panels (dose groups) with regard to ADP-induced platelet aggregation (IPA). Between group comparisons were performed on IPA and on bleeding times at the end of 30 minutes, 24 and 48 hours using ANOVA on ranked data.

The third objective of the trial was to provide estimates of clinical event frequencies from time of study initiation to hospital discharge in subjects with UAP/NQWMI. Given the low event rates, however, it was recognized that the study would not have sufficient power to detect clinically significant differences between the control and treatment groups.

a) Safety

Safety parameters included spontaneously reported adverse events and vital signs, which are summarized descriptively. Several important lab measurements including hematocrit, hemoglobin, and platelet count were also summarized.

For safety analysis, no statistical analyses were performed given the small number of events.

6.1.1.12 Efficacy Outcomes

6.1.1.12.1 Subject Demographics & Baseline Characteristics

The demographics of the treatment groups are shown below.

Table 6.1.1.6.1 Demographics of subjects enrolled in protocol #005.

	Tirofiban regimen [b]			Heparin
	Tirofiban 0.3/0.075 n=28	Tirofiban 0.4/0.1 n=23	Tirofiban 0.610.15 n=20	n=31
Sex				
Male	22 (79%)	22 (96%)	10 (100%)	26 (84%)
Female	6 (21%)	5 (22%)	10 (50%)	5 (16%)
Race				
White	24 (86%)	22 (96%)	20 (100%)	31 (100%)
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	4 (16%)	1 (4%)	0 (0%)	0 (0%)
Presentation				
Unstable angina	25 (89%)	18 (78%)	17 (85%)	28 (90%)
NQWMI	3 (11%)	5 (22%)	3 (15%)	3 (10%)
Ischemic ECG changes	16 (57%)	14 (61%)	14 (70%)	20 (65%)
Mean age (±SD)	63.9±11.3	61.8±9.9	66.5±7.8	64.2f9.7
Mean weight (±SD)	71.2±11.5	78.8±14.1	73.9±13.7	77.9±12.9

a. Data from NDA volume 1.40, Reference 4., Table 3.

b. Tirofiban groups shown as amount of bolus/ rate of infusion (in µg/kg/min).

6.1.1.12.2 Disposition of Subjects

Table 6.1.1.12.2.1 Summary of subject outcomes in protocol #005[a].

	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Heparin
Entered	28	23	20	31
Completed	27	22	19	28
Discontinued: Total	1	1	1	3
Clinical AEs	0	1	0	2
Laboratory AEs	0	0	0	0
Other	1	0	1	1

a. Data from NDA volume 1.40, reference 4, table 8.

6.1.1.12.2 Disposition of Subjects **(cont)**

The table below lists the discontinued subjects, along with the reasons for discontinuation

Table 6.1.1.12.2.1.2 Reasons for discontinuations

Treatment	Time Discontinued[b]	Reason for discontinuation
Tirofiban 0.3/0.075	4.75	Protocol deviation
Tirofiban 0.4/0.1	14	Clinical AE
Tirofiban 0.6/0.15	24	Protocol deviation
Heparin	13	Clinical AE
Heparin	6	Protocol deviation
Heparin	2.5	Clinical AE

a. Data from NDA volume 1.40, reference 4, table 9.
b. Hours after start of study drug

6.1.1.12.2b Protocol Violations & Deviations

Those subjects identified with protocol violations are listed in table 6.1.1.12.2.1.2 above.

6.1.1.12.2c Concomitant Therapies used after Trial Initiation

Concomitant medications were used by 95-100% of the subjects in all four groups. Of the concomitant medications used (see NDA volume 1.40, ref. 4, table 7) cardiovascular drugs were used by 275% of subjects in all groups. Overall, the use of concomitant medications was balanced across the 4 groups.

6.1.1.12.2d Primary Analyses of the Protocol **#005** Trial Results

Pharmacokinetics/ Pharmacodynamics

Only those subjects who received study drug and had measurements recorded at the specified protocol times were included in the analysis. A total of 10 subjects in the tirofiban groups, and five subjects in the heparin group were not included in the analysis of IPA due to missing values. All subjects who received heparin were pooled together for analysis.

Plasma tirofiban concentrations

The table below summarizes the tirofiban plasma concentrations for each dose group after 0.5 to 48 hours of infusion. A steady-state plasma concentration was achieved quickly following the bolus in all three groups and was maintained during the duration of the infusion.

Table 6.1.1.12.2d.1 Tirofiban plasma concentrations from protocol #005[a].

Infusion Time	Tirofiban 0.3/0.075 (N=27)*	Tirofiban 0.4/0.10 (N=20)*	Tirofiban 0.6/0.15 (N=16)*
0.5 Hours	34.06 ± 15.26	45.67 ± 13.71	73.47 ± 16.77
24 Hours	33.48 ± 10.34	48.56 ± 17.06	69.03 ± 20.42
36 Hours	31.96 ± 10.07	46.36 ± 17.21	68.82 ± 19.86
48 Hours	33.09 ± 10.22	52.59 ± 15.84	72.66 ± 20.98
Mean (24,36, & 48 hrs)	33.24 ± 10.38	48.66 ± 16.38	70.41 ± 20.05

a. Data from NDA volume 1.40, ref. 4, table 11.

Tirojban elimination rates

Clearance of tirofiban did not vary significantly across the three groups. However, subjects >65 years of age had a significantly lower systemic clearance of tirofiban than subjects ≤65. The sponsor attributed this difference to the decreased renal clearance in the elderly population (see protocol #014 review by Dr. Pellayo for details). The sponsor also examined the effects of concomitant use of medications on the clearance of tirofiban. While no significant effects were detected, the number of subjects taking each medication was small, limiting the power of this exploration to a 30% difference in clearance between the two groups.

Table 6.1.1.12.2d.2 Mean tirofiban plasma clearances from protocol #005[a].

	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Combined
Cls (ml/min) Combined	172.94±41.2	173.0±53.6	155.9±43.3	168.6
Cls (ml/min) ≤65	201.1 (n=13)	175.6 (n=13)	180.4 (n=5)	187.1[b]
Cls (ml/min) >65	146.7 (n=14)	168.3 (n=7)	144.8 (n=11)	168.6[b]

a. Data from NDA volume 1.40, ref. 4, table 12, and the final report for protocol #005.
b. The difference between the age groups was significant, p=0.008.

6.1.1.12.2d Primary Analyses of the Protocol **#005** Trial Results

Pharmacokinetics/ Pharmacodynamics(cont)

Inhibition ofplatelet aggregation (IPA)

The IPA was performed on all subjects with available data. In addition, 5 subjects had low levels of light transmission through their blood, making interpretation of IPA difficult. The significant differences between tirofiban and heparin persisted if these 5 subjects were excluded. At all time points, all subjects in the tirofiban groups had a greater IPA than the subjects in the heparin group.

Table 6.1.1.12.2d.3 Median IPA (%) from protocol #005[a,b].

Time of infusion	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Pooled Heparin
30 minutes	90.0*[b] (n=28)	89.6* (n=21)	96.0* (n=20)	-4.1 (n=30)
24 hours	88.2* (n=26)	82.9* (n=19)	93.6* (n=28)	-1.3 (n=26)
48 hours	78.3* (n=25)	86.3* (n=19)	92.1* (n=19)	1.2 (n=26)

a. Data from NDA volume 1.40, ref. 4, table 15, and the final report for protocol #005.
b. * values differ from pooled heparin value <0.05. There was no significant difference between the three tirofiban groups.

The next table shows the % of subjects who achieved ≥70% inhibition of IPA at the three time points. While a high percentage achieved >70% IPA in the tirofiban groups, shown below, 100% of the subjects in the heparin group failed to achieve this degree of IPA.

Table 6.1.1.12.2d.4 % of subjects achieving ≥70% IPA from protocol #005[a].

Time of infusion	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15
30 minutes	89.3 (n=28)	85.7 (n=21)	100 (n=20)
24 hours	76.9 (n=26)	68.4 (n=19)	100 (n=28)
48 hours	68.0 (n=25)	73.7 (n=19)	94.7 (n=19)

a. Data from NDA volume 1.40, ref. 4, table 17, and the final report for protocol #005.

Relationship of plasma concentration to IPA

Using the data from the plasma tirofiban concentrations and IPAs of individual subjects, the sponsor plotted the %IPA versus concentration. The estimated C_{50} for tirofiban was 15.5 ng/ml. The sponsor also noted that the average plasma concentration for the subjects in the trial (33 ng/ml in the 0.3/0.75 group, 49 ng/ml in the 0.4/0. 1 group) are on the steep part of the curve. This suggests that small changes in serum concentration may have a large effect on %IPA during the trials. For the 0.6/0.15 group, the mean concentration was 70 ng/ml, which is on the flat portion of the curve, suggesting this dose might be more stable as regards %IPA.

Template bleeding times

Bleeding times were next compared between the tirofiban groups and heparin at the end of 24 and 48 hours. Bleeding times were consistently prolonged in the tirofiban group, relative to the heparin group.

Table 6.1.1.12.2d.5 Median template bleeding times from protocol #005[a,b].

Time of infusion	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Pooled Heparin
24 hours	12.0* (n=23)	9.8* (n=22)	19.8* (n=20)	5.8 (n=28)
48 hours	13.8* (n=26)	13.0* (n=21)	15.4* (n=17)	7.5 (n=27)

a. Data from NDA volume 1.40, ref. 4, table 18, and the final report for protocol #005.
b. * values differ from pooled heparin value <0.05. There were no significant differences between the three tirofiban groups.

The bleeding times were also prolonged over baseline in the tirofiban groups. The table below shows the fold-change in bleeding time (Bleeding time extension, BTE) data when compared with baseline values.

Table 6.1.1.12.2d.6 Bleeding times extension (BTE) data from protocol #005[a,b].

Time of infusion	Tirofiban (0.3/0.075)	Tirofiban (0.4/0.10)	Tirofiban (0.6/0.15)	Pooled Heparin
24 hours	2.2* (n=23)	2.2* (n=22)	3.9* (n=20)	1.0 (n=28)
48 hours	2.6* (n=26)	2.6* (n=21)	3.3* (n=17)	1.3 (n=27)

a. Data from NDA volume 1.40, ref. 4, table 19, and the final report for protocol #005.
b. * values differ from pooled heparin value <0.05. There were no significant differences between the three tirofiban groups.

Pharmacokinetics/ Pharmacodynamics **(cont)**

Significantly, several subjects in the tirofiban groups had bleeding times 230 minutes (the longest period measured before the test was stopped). No subject in the heparin group had a similar prolongation of bleeding time.

Table 6.1.1.12.2d.7 Subjects with bleeding times 230 minutes from protocol #005[a].

Time of infusion	Tirofiban (0.3/0.075)	Tirofiban (0.4/0.10)	Tirofiban (0.6/0.15)	Pooled Heparin
24 hours	3/23 (13%)	2/22 (9%)	4/20 (20%)	0128 (0%)
48 hours	6/26 (23%)	4/21 (22%)	5/17) (23%)	0/27 (0%)

a. Data from NDA volume 1.40, ref. 4, table 20, and the final report for protocol #005.

Clinical Cardiac Events

The occurrence of clinical cardiac events was determined by the individual investigators, using the definitions in the protocol. No deaths were reported during the study period. The table below shows the occurrence of other clinical adverse events. The mean duration of hospitalization was 11.1±6.4 days in the study.

Table 6.1.1.12.2d.8 Refractory ischemia, myocardial infarctions, and recurrent angina in protocol #005[a].

Clinical event shown as # of subjects (% of all subjects)	Tirofiban 0.3/0.075 n=28	Tirofiban 0.4/0.1 n=23	Tirofiban 0.6/0.15 n=20	Pooled Tirofiban n=71	Pooled Heparin n=31
Hour 48					
Refractory ischemia	1 (4)	0 (0)	0 (0)	1 (1)	3 (10)
Myocardial Infarction	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Recurrent angina	7 (25)	4 (17)	9 (45)	20 (28)	9 (29)
Hospital Discharge					
Refractory ischemia	3 (11)	0 (0)	0 (0)	3 (4)	4 (13)
Myocardial Infarction	0 (0)	0 (0)	1 (5)	1 (1)	1 (3)
Recurrent angina	14 (50)	10 (43)	10 (50)	34 (48)	15 (48)

Data from NDA volume 1.40, ref. 4, table 21and 22, and electronic datasets.

Similarly, the number of cardiac procedures prior to discharge were collected in the four groups, and the results are shown below. Coronary angiography was a common procedure in all groups, with slightly fewer subjects undergoing PTCA and/or CABG.

Table 6.1.1.12.2d.9 Cardiac procedures in protocol #005[a] prior to discharge.

Clinical event shown as # of subjects (% of all subjects)	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Pooled Tirofiban	Pooled Heparin
Hospital Discharge					
Coronary angiography	14 (50)	15 (65)	12 (60)	41 (58)	18 (58)
PTCA	6 (21)	7 (30)	5 (25)	18 (25)	6 (19)
CABG	3 (11)	3 (13)	5 (25)	11 (15)	4 (13)
Any revascularization	9 (32)	10 (43)	9 (45)	28 (39)	10 (32)

a. Data from NDA volume 1.40, ref. 4, table 23, and electronic datasets.

6.1.1.13 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. There was no apparent dose-related effect of tirofiban on any safety measure.

Table 6.1.1.13.1 Clinical adverse experience summary from protocol #005[a].

Clinical event shown as # of subjects (% of all subjects)	Tirofiban 0.3/0.075	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Pooled Heparin
With Any Adverse Experience	14 (50)	10 (43)	4 (20)	10 (32)
Without Any Adverse Experience	14 (50)	13 (57)	16 (80)	21 (68)
With Serious Adverse Experience	3 (11)	1 (4)	3 (15)	2 (6)
With Drug-Related Adverse Experiences[b]	4 (14)	1 (4)	1 (5)	3 (10)
With Serious and Drug-Related Adverse Experiences	0 (0)	1 (4)	0 (0)	1 (3)
Discontinued due to an Adverse Experience	0 (0)	1 (4)	0 (0)	2 (6)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

a. Data from NDA volume 1.40, ref. 4, table 24, and electronic datasets.
b. Felt to be possibly, probably, or definitely drug-related by individual investigators.

6.1.1.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

6.1.1.13.2 Comments on Specific Safety Parameters

Deaths

There were no subject deaths.

Tirofiban overdose:

One individual received an overdose of tirofiban, and his case report summary is below.

A 63-year-old male patient (AN 184) who presented with unstable angina pectoris was placed on therapy with tirofiban (0.4 µg/kg/min for 30 minutes; 0.1 µg/kg/min for 47.5 hours). Therapy was discontinued due to overdosage of MK-0383 in which the patient received 0.4 µg/kg/min for 14 hours. The patient did not develop abnormal signs or symptoms following overdose and no bleeding complications were reported. PTT and PT were normal. All other lab values were normal. Concomitant therapy was metoprolol, ASA, nitroglycerin and heparin. No plasma MK-0383 concentration was actually drawn at the end of the infusion.

Bleeding AEs

No subject required transfusion as the result of a bleeding episode in protocol #005. Details of bleeding AEs in the tirofiban NDA are found in sections 8.1 and 8.2. Overall, there were no serious episodes of bleeding in protocol #005, and no discontinuations for bleeding AEs. The incidence of bleeding AEs was also similar in the two groups: 4/7 1 (6%) for tirofiban and 213 1 (6%) for heparin.

6.1.1.14 Protocol #005 Efficacy Summary

This study was designed to assess the pharmacokinetics of tirofiban in subjects with UAPMQWMI, and to compare the effect of tirofiban on coagulation parameters with that of heparin.

Pharmacokinetics

The clearance of tirofiban was similar in all three doses examined in the protocol. Subjects >65 had a smaller clearance of tirofiban, perhaps related to diminished renal clearance, an important pathway for tirofiban clearance.

In all subjects, the bolus and infusion of tirofiban achieved high plasma concentrations of tirofiban within 30 minutes. No information about the plasma levels between 30 minutes and 24 hours are available. The plasma levels were stable at 24 and 48 hours in all tirofiban groups.

Phatmacodynamics

The doses of tirofiban used in the protocol cause a >70% inhibition of platelet aggregation in almost all subjects, and had a significantly greater effect than did heparin. The two lower doses of tirofiban were less consistent in their effect on platelet inhibition, when compared with the highest dose (0.6 µg/kg bolus followed by a 0.15 µg/kg/min infusion) (see table 6.1.1.12.2d.4). There is also a suggestion that the highest dose (0.6/0.15) used had a greater effect to prolong bleeding time at the end of 24 hours. For instance, table 6.1 .1.12.2d.6 shows that the 0.6/0.15 tirofiban group had a greater effect on BTE at the end of 24 hours than other tirofiban groups. Similarly, a higher percentage of subjects had bleeding times 230 minutes in the 0.6/0. 15 dose group (table 6.1 .1.12.2d.7).

Clinical endpoints

No inferences as to the efficacy of tirofiban can be drawn from the small numbers of clinical events. The population enrolled in the trial underwent cardiac procedures, including angiography, PTCA and CABG

6.1.1.15 Protocol #005 Safety Summary

The small number of subjects makes overall assessment of safety difficult. There were no unexpected toxicities detected, and the bleeding AEs occurred at a similar frequency in the tirofiban and heparin groups.

6.1.1.16 Protocol #005 Reviewer's Conclusions

1. Systemic clearance of tirofiban is independent of the doses used in this study.

2. Tirofiban produces a >70% inhibition of ADP-induced platelet aggregation (IPA) in a high percentage of subjects at the doses used. The highest dose regimen has a more consistent effect on IPA when compared with the other two dosing regimens, but may also has a greater effect to prolong bleeding time.

3. No safety issues were identified in this small database.

6.1.2 Review of Protocol #007

6.1.2.1 Title of Study

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of MK–0383 in High-Risk Patients Undergoing Percutaneous Transluminal Coronary Angioplasty (Protocol #007).

6.1.2.2 Sites of Investigation and Investigators

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

The RESTORE trial was conducted at 9 sites in the United States.

6.1.2.3 Background

Initial nrotocol submitted:	8.12.93
First nrotocol amendment submitted:	10.22.93

This amendment allowed the entry into the trial of subjects undergoing atherectomy.

Subiect entry:	10.4.93 to 2.24.94
Case report form cutoff	4.29.94

6.1.2.4 Study Design

This was a randomized, double-blind, placebo-controlled, multicenter, multinational study. It was designed to:

1) 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);

2) study the pharmacokinetics and pharmacodynamics of tirofiban on a background of ASA and heparin;

3) investigate the incidence of adverse cardiac events (need for urgent revascularization, nonfatal MI, or death) within 24 hours after successful angioplasty and during subsequent hospitalization.

Subjects were studied in three separate panels (24 subjects/panel). Subjects were randomized to receive tirofiban or placebo in a 3: 1 ratio for 16 to 24 hours, and then were followed throughout the hospitalization.

All subjects received open-label heparin (dosage and administration determined by the investigator with protocol guidelines) and open-label aspirin.

All patients considered potential candidates for the study- were required to have undergone diagnostic coronary angiography for characterization of coronary anatomy and for determining the course of therapeutic intervention prior to the study procedure. This diagnostic catheterization could have taken place prior to the hospital admission for angioplasty, but needed to be recent (within 2 months with no new antecedent coronary events). Once the cineangiograms were reviewed and the patient was determined to be eligible for the study, randomization could then occur. Patients were required to be randomized within 72 hours prior to the angioplasty. Angioplasty procedures followed the standard procedures for the site. In general, the heparin bolus was given after sheath placement and approximately 15 minutes prior to administration of study drug. Catheters were then placed. Tirofiban (or placebo) was administered as a bolus at least 5 minutes prior to balloon inflation and the maintenance infusion was initiated immediately following the bolus. The maintenance infusion was continued for at least 16 hours, but not more than 24 hours. This 8-hour window was provided to allow flexibility in the scheduling of platelet aggregation tests with the local laboratory. These studies were timed from the point of study drug cessation and continued for 8 hours after termination of the study drug infusion. A heparin maintenance infusion was started after completion of the procedure, before the patient left the catheterization laboratory, and was discontinued simultaneously with the tirofiban infusion. Catheterization sheaths were pulled no less than 4 to 6 hours after cessation of the study drug and heparin infusions, unless otherwise deemed necessary by the principal investigator.

6.1.2.4 Study Design (cont)

Baseline Period

Patients underwent a medical history review and received a complete physical examination within 72 hours prior to the scheduled angioplasty. Patients were weighed and the following tests was performed as detailed below, Upon randomization or within 12 hours prior to balloon inflation, each patient received aspirin 325 mg orally. Aspirin was required to be administered at least 1.5 hpurs before doing the baseline bleeding time, which was to have been performed prior to entering the catheterization laboratory. Template bleeding time (BT) was performed within 4 hours prior to balloon inflation on the arm that did not have indwelling lines. On the day of the procedure, if the patient did not have venous access, an indwelling intravenous cannula was inserted for infusion of heparin and study drug.

Double-Blind Treatment Period, Hours 0 to 24

PTCA or activation of the atherectomy device was to have occurred no later than 72 hours after completion of all baseline examinations performed pre-catheterization. Angioplasty was performed according to institutional guidelines and standards. After placement of sheaths, blood for ADP-induced platelet aggregation was drawn. Pre-angioplasty, heparin was administered as a 10,000 U bolus or was weight-dosed at 150 U/kg if the patient weighed less than 75 kg. Five minutes after administration of heparin, a second ADP sample and tirofiban plasma level were drawn. Fifteen minutes after the heparin bolus, study drug was initiated. Immediately after completion of the bolus (5 minutes), another ADP-induced platelet aggregation and tirofiban level were drawn. Upon completion of these blood samples, the initial balloon inflation (or initiation of the atberectomy device) occurred. Additional heparin boluses could be given in 2000 U increments during the procedure to maintain the activated clotting time (ACT) between 300 to 350 seconds at the discretion of the- angioplasty team. The patient was observed for at least 20 minutes after the final inflation to ensure stability prior to leaving the laboratory. Prior to leaving the catheterization laboratory, a heparin maintenance infusion of 1000 U/hour was initiated to run simultaneously with the tirofiban infusion. If the patient weighed less than 75 kg, the heparin drip was weight-dosed at 15 U/kg/hour. Aspirin, 325 mg orally, was administered 24 hours after the pre-procedure dose and then daily thereafter (at a dose determined by the patient's physician). Other tests were performed as indicated below.

Study drug and heparin were simultaneously discontinued between 16 and 24 hours of infusion. Sheaths were removed no less than 4 to 6 hours after discontinuation of the heparin and study drug infusions, unless otherwise deemed necessary by the principal investigator. Institutional guidelines for post-PTCA ambulation after sheath removal were followed. Oral, sublingual, topical, or intravenous nitrates could be administered at the discretion of the treating physician. Calcium channel blockers and beta-blockers could also be given if necessary. If the patient was receiving and tolerating an agent from these classes of drugs prior to balloon angioplasty, the same agent could be continued throughout and after the PTCA or atherectomy. All nonstudy medications received during the procedure and for 10 hours after completion of study drug were recorded on the case report forms. Warfarin, nonsteroidal anti-inflammatory agents, or other anticoagulants were not to be instituted until 24 hours after sheath removal. No other antiplatelet (except aspirin) or anticoagulant drugs (except heparin) were permitted until IO hours after sheath removal. Intravenous antiarrhythmic therapy prior to balloon angioplasty was a study exclusion criterion. During the infusion of study drug, for 10 hours following completion of study drug, and until hospital discharge (or Day 7 after PTCA), all clinical events were documented on the case report forms.

6.1.2.5 Primary and Secondary Endpoints

The primary aim of the study was to collect pharmacokinetic and pharmacodynamic data, including:

1) Serial tirofiban serum concentrations;
2) Serial measurements of the % inhibition of ADP-induced aggregation; and
3) Serial measurements of the extension of bleeding times.

While not powered to detect differences in clinical endpoints, the study did collect information about the following clinical events:

1) Ischemic episodes;
2) Refractory angina pectoris;
3) Myocardial infarction;
4) Need for urgent cardiac revascularization; and
5) Death.

6.1.2.6 Number of subjects/ randomization

Three panels of 24 subjects in each panel were to be enrolled, beginning with the lowest dose of tiroflban and proceeding to the next dose after evaluation of the results from the first panel by the sponsor. The actual number of subjects randomized is shown below.

Table 6.1.2.6.1 Summary of subjects entered into each dose group in protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Placebo +Heparin
Entered	21	30	22	20

a. Data from NDA volume 1.46, reference 6, page 5456.

6.1.2.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1) Patients of either sex were eligible for inclusion into the study if they were scheduled to undergo angioplasty for:

a) Recurrent rest angina in patients with unstable angina. Onset of symptoms needed to be within 5 days of the initial presentation with unstable angina. For the purposes of this study, patients will be defined as having refractory angina if the angina occurs as a single episode persisting for 220 minutes, or ≥2 episodes persisting for ≥10 minutes each, or marked ECG changes (new ST-segment elevation or depression 20.2 mV in two contiguous leads) in the presence of what the investigator determines to be full medical therapy. Full medical therapy should include at least an infusion of nitroglycerin plus a beta-blocker or calcium antagonist, titrated to heart rate and blood pressure.

b) Recurrent angina 24 hours or more after an acute myocardial infarction. Onset of symptoms needed to be within 5 days of the infarction.

c) Complex coronary artery lesion morphology-American Heart Association/American College of Cardiology lesion types B or C: Type B lesions include lesions that are tubular in shape, eccentric, have tortuosity of the proximal segment, are located in a moderately angulated segment (>45° and <90°), have an irregular contour, moderate or severe calcification, or have thrombus present. Also included would be ostial lesions, bifurcation lesions requiring double guide wires, and total occlusions <3 months old. Type C lesions have the following characteristics: diffuseness (>2 cm in length), excessive tortuosity of proximal segments, location in an extremely angulated segment (>90°), total occlusion >3 months old, inability to protect major side branches, and degeneration of older vein grafts with friable lesions. In addition, patients had to have undergone diagnostic coronary angiography. If the diagnostic catheterization was done in a prior hospital admission, it needed to be recent (within 2 months of study start) and with no new antecedent coronary events.

2) Subjects were to be 18-75 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 and women of childbearing potential.

2) Thrombolytic therapy within 24 hours prior to the angioplasty.

3) Severe multivessel disease with diffuse severe atherosclerosis or presence of a >50% left main lesion unprotected by bypass grafts.

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

5) Patients receiving oral anticoagulant medications (i.e., warfarin) within 1 week prior to randomization or antiplatelet agents (except aspirin) within 12 hours (such as nonsteroidal anti-inflammatory agents, dipyridamole, and sulfmpyrazone). Patients receiving ticlopidine within 1 week prior to randomization were not be eligible for inclusion in the study.

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

7) Patients with uncontrolled severe cardiac arrhythmias, including persistent sinus tachycardia >120 beats/minute, or any patient requiring intravenous antiarrhythmic therapy prior to balloon angioplasty.

8) Patients needing intra-aortic balloon counter pulsation for relief of ischemia.

6.1.2.7 Inclusion/ Exclusion Criteria **(cont)**

Exclusion Criteria **(cont)**

9) Contraindications to anticoagulation:

a) Past or present bleeding disorder including a history of gastrointestinal bleeding, hematuria, or presence of occult blood in the stool at the time of randomization. Any patient with a known platelet disorder, history of thrombocytopenia, or previous exposure to a fibrinogen receptor antagonist was also 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. Patients with transient ischemic attacks within 1 year of study start were also excluded.

d) Prolonged cardiopulmonary resuscitation within the 2 weeks prior to randomization.

e) Severe physical trauma within 6 months prior to randomization.

f) Major surgery or biopsy (noncutaneous) within 3 months prior to enrollment.

g) Active peptic ulcer disease within 3 months prior to randomization.

h) Probable pericarditis.

i) Presence of significant retinopathy (i.e., hemorrhages or exudates).

IO) History of recent or ongoing alcohol abuse or other drug abuse.

11) Patients with acute pulmonary edema (rales present over more than 50% of the lung fields) or patients with severe congestive heart failure (New York Heart Association Functional Class III or IV).

12) Sustained supine, sitting, or standing systolic blood pressure <95 mmHg or evidence of cardiogenic shock at randomization.

13) Patients with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.

14) Patients with uncontrolled diabetes mellitus or other uncontrolled endocrinopathy.

15) Patients with important systemic renal, pulmonary, hepatic, neurological, or hematological disorders.

16) Patients with clinically important abnormal laboratory findings including:

a) Serum creatinine >2.0 mg/dL.

b) Hemoglobin <12 gm/dL or hematocrit <36%.

c) Platelet count <150,000/mm^3.

d) Prothrombin time (PT) or activated partial thromboplastin time (aPTT) >1.2X laboratory control. For patients already receiving heparin at the time of enrollment, the requirement that the baseline aPTT must be >1.2X laboratory control is waived. However, the baseline PT must be 21.2X laboratory control and the baseline bleeding time must be ≥12 minutes. In addition, the baseline fibrinogen level must be within the laboratory normal range (e.g., 200 to 400 mg/dL) for all patients.

e) Template bleeding time >12 minutes.

f) Patient's weight >300 lbs.

17) Patients receiving another investigational drug within 4 weeks prior to randomization.

18) 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 patient.

19) Inability to give informed consent.

6.1.2.8 Dosage/ Administration

Three panels were studied sequentially, and were assigned increasing doses of tirofiban, unless clinically significant adverse events, such as bleeding, were observed. In the first panel, patients randomized to receive tirofiban received an intravenous tirofiban bolus of 5 mg/kg over 5 minutes, immediately followed by a maintenance infusion at 0.05 mg/kg/minute for 16 to 24 hours (tirofiban 5/0.05). Patients in the second panel received an tirofiban bolus of 10 mg/kg over 5 minutes, immediately followed by a maintenance infusion at 0.10 mg/kg/minute for 16 to 24 hours (tirofiban 10/0.10). In the third panel, patients received a bolus of 10 mg/kg over 5 minutes, immediately followed by a maintenance infusion of 0.15 mg/kg/minute for 16 to 24 hours (tirofiban 10/0.15). (A protocol amendment decreased the original panel III bolus dose from 15 mg/kg to 10 mg/kg). The dose of the maintenance infusion remained as originally proposed.) All patients received open-label heparin in accordance with guidelines provided to the investigators. Heparin was administered concomitantly with the tirofiban/placebo infusion. Additionally, all patients received aspirin 325 mg orally at randomization and then daily thereafter. Other therapies (nitrates, beta blockers, calcium channel blockers, etc.) were administered if deemed necessary by the principal investigator.

6.1.2.9 Duration/ Adjustment of Therapy

Study drug was discontinued for clinically relevant hemorrhage, a significant decrease (>5.0 g/dL) in blood hemoglobin or significant thrombocytopenia. If at any time the platelet count dropped to 100,000/mm^3 or decreased to 60% of the pre-drug value, the test was repeated immediately. If the platelet count decreased to <90,000/mm^3 the infusion of study drug and heparin was discontinued, and two additional tubes of serum were collected and analyzed for antiplatelet and antidrug antibodies against tirofiban or heparin by an independent laboratory. In addition, study drug was to be discontinued for any of the following reasons:

1) A condition that necessitated thrombolytic therapy, including acute closure during PTCA or atherectomy.
2) Progression to myocardial infarction.
3) Need for emergent coronary artery bypass surgery, repeat angioplasty, atherectomy, or stent placement.
4) Need for intra-aortic balloon counter pulsation or percutaneous bypass.

6.1.2.10 Safety and Efficacy Endpoints Measured

Table 6.1.2.10.1 ' metable f . clinical observation and lab mea urements the protocol 107".

	Baseline ≤72 hours	Precath 512 hours	Sheath--- -20 mins	Heparin -15 mins	Study Drug -10 mins	Balloon inflation O-5 mins	2 hrs	6 hrs	12 hrs	16-24 hrs
History	X									
Physical	X									X
CXR	X									
ECG	X									X
Plasma tirofiban					X	x	X			X
IPA			x		X	x	X			
Bleeding time		X								X
PT/PTT	X							X	X	X
Compete labs'	X									X
Hbg/Hct/Plt #							X	X		
BP and HR										
Clinical events										
ASA		X							d	
Heparin bolus				:X						
Heparin infusion[b]										
Study drug bolus'					X					
Study drug infusion										

a. Data om NDA v ime 1.46, reference 7, table 1A.
b. Hepa i dosed per standard prac e with protocol-specified guidelines. Heparin was started after the beginning of the study drug.
c. Study drug was administered by bolus beginning at approximately time 0, followed by the infusion.
d. The second ASA dose was administered 24 hours after the pre-PTCA dose.
e. Lab work included: (1) A complete blood count (hemoglobin, hematocrif white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis) and (4) Stool for occult blood (as available),

Clinical Cardiac Events

Although the trial was not powered to detect differences in event rates, the following clinical events were monitored:

1) Ischemic Episodes

All patient-reported episodes of angina and adjustments or additions of anti-angina1 medications were recorded. The nurse was provided with a form to capture the following information: the time, severity, and duration of angina; any increase *or* decrease in antianginal medication; and the amount and type of additional anti-angina1 medication needed to relieve angina1 symptoms. Any non-routine electrocardiograms were also recorded and reported.

2) Refractory Angina Pectoris

Refractory angina pectoris was defmed as the presence of angina1 chest pain with ischemic ST-T changes (new ST-segment depression or elevation of 20.1 mV or T-wave inversion in two contiguous leads on a 12-lead ECG) occurring as a single episode persisting for ≥20 minutes, or greater than or equal to two episodes persisting for ≥10 minutes each, despite full medical therapy [including at least an infusion of nitroglycerin plus a beta-blocker or calcium antagonist, titrated to heart rate and blood pressure). All angina that met the criteria of refractory angina was clearly noted on the case report form.

6.1.2.10 Safety and Efficacy Endpoints Measured (cont)

3) Myocardial Infarction

Additional creatine kinase measurements were to be obtained immediately after each episode of typical ischemic chest pain lasting 10 minutes or more and were repeated 6 hours later. The development of myocardial infarction 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 greater than two times the upper limit of normal. In patients enrolled with a non-Q-wave myocardial infarction, a new infarction was defmed as a rise in creatine kinase to 250% above the preceding sample and was at least greater than or equal to two times the upper limit of normal and not associated with the original event.

4) Revascularization

Although not explicitly discussed in the protocol, all coronary revascularization procedures PTCA or CABG during the hospitalization were recorded on the case report form.

6.1.2.11 Statistical Considerations

The primary hypotheses in protocol #008 were:

1 .The pharmacokinetic parameters of tirofiban (i.e., systemic clearance (CL,), volume of distribution (Vd_{ss}) and half-life ($t_{1/2}$), when administered with heparin will not differ from those observed in tirofiban alone in historical controls.

Power

The sponsor calculated that there will be 80% power (alpha=0.05, two-tailed) to detect the following differences in parameter estimates between the 18 patients in each panel of this trial and the 46 subjects on tirofiban and aspirin in previous tirofiban trials without concurrent heparin dosage (preliminary information from protocol 004 or protocol 005): 19% in systemic clearance (CL,); 21% in volume of distribution (Vd_{ss}); and 10% in half-life. The protocol specified that, if all three panels are completed and the patient demographic characteristics and responses indicate that the data can be pooled, the above parameters would be estimated from the data in all three panels combined. Thus, with the 54 planned patients in this trial, pooled together, and the 46 subjects from the previous trials, there will be 80% power (alpha =0.05, two-tailed) to detect the following differences: 14% in systemic clearance; 16% in volume of distribution; and 7% in half life. These estimates are based on means and standard deviations in preliminary data from protocol 004 for half-life (2.03 ± 0.26 hours), volume of distribution (70 4 19 liters), and systemic clearance (242 ± 60 ml/minutes).

2. When administered with heparin, the concentration of tirofiban that produces an ADP-induced platelet inhibition of 50%, i.e., the C_{50}, will not differ from that observed with tirofiban alone in historical controls.

Power

The sponsor calculated that there will be 80% power (alpha level =0.05, two-tailed) to detect a 23% difference in C_{50} between the 54 subjects on tirofiban and heparin in this trial and the 46 subjects on tirofiban alone (protocols 004 and 005). This estimate is based on the mean and standard deviation from preliminary data from tirofiban protocol 004 for C_{50} of 20 ± 8 ng/ml.

3. When tirofiban is administered with heparin in patients undergoing PTCA, it will be safe enough to proceed with future studies.

Power

If none of the 18 patients in a treatment group experience an event, then it can be assumed with 80% confidence that the incidence rate of that event is less- than 12%. If 1 patient experiences an event, then it can be assumed with 80% confidence that the incidence rate is less than 20%. This study is not powered to determine if there are statistically significant differences among the three tirofiban dosage groups in the incidence of clinical events.

Multiplicity

No multiplicity adjustments were stipulated by the protocol. No multiplicity adjustments were made and all tests were performed at the 5% level of significance.

6.1.2.11 Statistical Considerations (cont)

Exploratory Analyses

The effect of age and renal function on the systemic plasma clearance of tirofiban were studied.

Interim Analyses

No formal interim analyses were stipulated by the protocol and none were performed.

Statistical Analysis

1) Approaches to Analysis

The statistical analysis of pharrnacokinetic and efficacy data followed a "per-protocol" approach. Only patients who were currently on drug at the time window specified in the protocol were included in the analysis. Missing measurement values were not estimated.

All patients were included in the analysis of safety data. In the presentation of summary statistics for vital signs measurements, values for time points during infusion were included at that time point only if the patient was still being infused.

2) Statistical Methods for protocol #007

Pharmacokinetics

Systemic plasma clearance of the drug was compared among the three tirofiban panels and with heparin only using an ANOVA model that included factors for dose, age, and creatinine clearance as well as all two-way interactions. Gender was not factored in given the small number of females. The relationship between creatinme clearance and age and between creatinine clearance and systemic plasma drug clearance was investigated using regression and Spear-man's rank correlation. Analysis of variance was used to evaluate the effect of heparin on systemic plasma drug clearance, by comparing the high- and low-dose groups in this study (tirofiban + heparin) with the corresponding dose groups in protocol 005 (tirofiban in the absence of heparin). Results from this analysis should be viewed with caution since they may contain bias due to potentially different patient populations and study conditions, nonrandomization, and other concerns inherent in comparing to a historical control.

Pharmacodynamics

An analysis of percent inhibition of platelet aggregation (IPA [%]) was completed on 5 mM ADP light transmission data. Primary efficacy endpoints included the IPA (%) at the end of the bolus infusion (0.5 hours) and at the end of the sustained infusion (48 hours). Because many subjects on tirofiban approached 100% inhibition of ADP-induced platelet aggregation, the data are not normally distributed. Therefore, medians instead of means and nonparametric methods were used to draw inference about platelet inhibition in the general patient population.

Pharmacodynamic Efficacy - Comparison of IPA with Plasma Concentration

Plasma concentrations for the two panels across all time points were plotted against the corresponding values of IPA for the respective time points. Pooled IPA (%) and tirofiban concentrations from patients in the two-dose panels were fit to a sigmoid E_{max} model to allow calculation of the C_{50} (the concentration that yields 50% IPA) and the Hill coefficient. The model assumed that E_{max} was 100% inhibition.

Pharmacodynamic Efficacy - Bleeding Times

Another measure of drug efficacy in preventing platelet aggregation was template bleeding time. Bleeding time extension (BTE) was calculated by dividing each template bleeding time by the template bleeding time predose (-0.5 hours).

Clinical Cardiac Events

The incidence rates for clinical cardiac events (progression to myocardial infarction, urgent revascularization, and/or death) during study infusion and at hospital discharge were tabulated. All repeat catheterizations were also recorded.

Safety

Safety parameters included spontaneously reported adverse events and vital signs, which are summarized descriptively. Several important lab measurements including hematocrit, hemoglobin, and platelet count were also summarized.

6.1.2.12 Efficacy Outcomes for protocol **#007**

6.1.2.12.1 Subject Demographics **&** Baseline Characteristics

The demographic and clinical background data for the 93 subjects enrolled in protocol #007 are summarized below.

Table 6.2.3.12.1.1 Demographics of protocol #007[a].

Demographic	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Placebo +Heparin
Total Randomized	N=21	N=30	N=22	N=20
Gender	n (%)	n (%)	n (%)	n (%)
Male	20 (95)	22 (73)	19 (86)	15 (75)
Female	1 (5)	8 (27)	3 (14)	5 (25)
Race (n (%))				
Caucasian	17 (81)	26 (87)	20 (91)	17 (85)
Black	1 (5)	2 (7)	0 (0)	2 (10)
Hispanic	3 (14)	2 (7)	2 (9)	1 (5)
Presentation				
Unstable Angina	2 (10)	2 (7)	1 (5)	0 (0)
Unstable Angina + Complex Lesion	4 (19)	14 (47)	7 (32)	6 (30)
Complex Lesion (type B or C) only	11 (52)	8 (27)	14 (64)	11 (55)
Post-MI Angina + Complex Lesion	4 (19)	6 (20)	0 (0)	3 (15)
Extent of Disease				
Single Vessel	8 (38)	13 (43)	5 (23)	7 (35)
Double Vessel	5 (24)	7 (23)	9 (41)	8 (40)
Triple Vessel	5 (24)	6 (20)	7 (32)	3 (15)
Left Main Disease	0 (0)	1 (3)	0 (0)	1 (5)
Graft Stenosis	4 (19)	1 (3)	1 (5)	1 (5)
Procedures Performed				
Balloon Angioplasty	16 (76)	24 (82)	15 (68)	14 (70)
Atherectomy	2 (10)	2 (7)	4 (18)	1 (5)
Angioplasty + Atherectomy	1 (5)	2 (7)	3 (14)	4 (20)
No Procedure[b]	2 (10)	2 (7)	0 (0)	1 (5)
# of Sites Dilated	1 7 (33)	9 (30)	8 (36)	5 (25)
	2 5 (24)	8 (27)	9 (41)	8 (40)
	≥3 7 (33)	9 (30)	4 (18)	5 (25)
Vessel Dilated				
Left Anterior Descending	14 (67)	10 (33)	11 (50)	10 (50)
Circumflex/Marginal	8 (38)	15 (50)	9 (41)	7 (35)
Right Coronary Artery	9 (43)	14 (47)	11 (50)	10 (50)
Mean Age (±SD)	55 (±12)	61 (±10)	58 (±11)	60 (±10)
Age Range (Years)	22-71	43-78	38-79	37-73
Mean Weight, kg (±SD)	89 (±19)	84 (± 17)	86 (± 16)	89 (± 21)
Weight Range (kg)	59-148	55-115	61-132	53-133

a. Data from NDA volume 1.45, reference 6, table 4.

b. Four tirofiban subjects and one placebo subject had no procedure performed.

6.1.2.12.1 Subject Demographics & Baseline Characteristics **(cont)**

Table 6.2.3.12.1.2 Antecedent history of coronary artery disease in protocol #007[a].

Demographic	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Placebo +Heparin
Total Randomized	N=21	N=30	N=22	N=20
Stable Angina Pectoris (number and %)	15 (71)	28 (93)	14 (64)	13 (65)
Unstable Angina	10 (48)	22 (73)	8 (17)	9 (45)
Myocardial Infarction	8 (38)	13 (43)	11 (50)	11 (55)
Coronary Artery Bypass Surgery	5 (24)	3 (10)	3 (14)	2 (10)*

a. Data from NDA volume 1.45, reference 6, table 5.

6.1.2.12.2 Disposition of Subjects

Fewer subjects in the high-dose group completed the trial, with 5/7 drop-outs in this group being due to clinical AEs.

Table 6.1.2.12.2.1 Summary of subjects entered into each dose group in protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Placebo +Heparin
Entered	21	30	22	20
Completed	19 (90.5%)	28 (93.3%)	15 (68.2%)	17 (85%)
Discontinued: Total	2	2	7	3
Clinical AEs	1	0	5	1
Laboratory AEs	0	0	1	0
Other	1	2	1	2

a. Data from NDA volume 1.46, reference 6, page 5456.

The reasons for discontinuation are listed below. Note that 4/7 of the discontinuations in the hi&dose tirofiban group were related to bleeding.

Table 6.1.2.12.2.2 Reasons for discontinuation in protocol #007[a].

Treatment Group	Patient #	Infusion Duration (hrs)	Reason for Discontinuation
Tirofiban (5/0.05)			
	016	1.6	Clinical Adverse Experience - Bleeding
	055	1.1	Failed Angioplasty / Closure
Tirofiban (10/0.10)			
	133	11.9	Protocol Deviation
	165	1.6	Unable to cross lesion
Tirofiban (10/0.15)	210	1.1	Clinical Adverse Experience
	221	5.2	Clinical Adverse Experience - Bleeding hemoptysis, post-op bleeding, decreased Hct
	233	12.7	Protocol Deviation
	241	9.4	Clinical Adverse Experience - Bleeding retroperitoneal hemorrhage
	242	14.9	Laboratory Adverse Experience decreased platelets
	250	4.2	Clinical Adverse Experience
	261	3.6	Clinical Adverse Experience - Bleeding
Placebo	017	0.2	Other - Patient Uncooperative
	101	2.8	Clinical Adverse Experience
	155	1.7	Other - Protocol Deviation

a. Data from NDA volume 1.46, ref. 6, table 10.

›. Note: AN 221 had a discontinuation for Clinical Adverse Experiences - "Hemoptysis" and "Bleeding, post-op." The patient also had a Laboratory Adverse Experience, "Decreased hematocrit," noted as a reason for discontinuation. AN 241 had a discontinuation for the Clinical Adverse Experiences "Hematoma" and "Hemorrhage, retroperitoneal." The patient also had a Laboratory Adverse Experience, "Decreased hematocrit," noted as a reason for discontinuation. AN 242 had a discontinuation for the Laboratory Adverse Experience "Platelets decreased" but also had Clinical Adverse Experiences "Hematoma" and "Bleeding, post-op" noted as reasons for discontinuation.

6.1.2.12.2a Subject **Selection**

No information is available about subject selection in protocol 007.

6.1.2.12.2b Protocol Violations **&** Deviations

1. Subject AN 110 was randomized to receive a maintenance infusion of 0.1 µg/kg/min, but received 0.14 µg/kg/min. Her data was excluded from the pharmacokinetic and pharmacodynamic datasets.

2. Several subjects (19/93, 20.4%) terminated their study drug infusion prior to 16 hours (the protocol-stated minimum). Post-hoc, the sponsor determined that 9.5hours was the minimum duration of infusion to include subjects in the analysis, since they calculated that steady-state levels of tirofiban would be reached by that time. A total of 10 subjects were thus excluded (3 placebo, 7 tirofiban).

3. Several subjects or portions of their data sets were excluded due to several reasons: no measurement done; early termination or infusion; measurement of time point out of specified range; or measurement was done at an additional time point. The breakdown of these excluded are shown below.

	Tirofiban 510.5 +Heparin	Tirofiban 1010.1 +Heparin	Tirofiban 1010.15 +Heparin	Placebo +Heparin
Subjects (%)	5/21 (24%)	17/30 (57%)	9/22 (41%)	11/20 (55%)

6.1.2.12.2c Concomitant Therapies used after Trial Initiation

The most frequently used agents (beta blockers, heparin, calcium-channel blockers, nitrate preparations, aspirin) reflect the underlying coronary disease of this population undergoing angioplasty (>85% of subjects in all four groups were taking cardiovascular drugs). There were no significant differences in the frequency of use for any concomitant medications (see NDA volume 1.46, ref. 6, table 8 for details).

6.1.2.12.2d Primary Analyses of Protocol **#007** Trial Results

Pharmacokinetics/ Pharmacodynamics

Plasma tirofiban concentrations

The first table shows the average plasma tirofiban levels during the trial.

Table 6.1.2.12.2d.1 Plasma tirofiban concentrations during protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin
Post-bolus	24.1 ± 9.3 (n=17)	65.3 ± 26.8 (n=25)	64.2 ± 24.2 (n=19)
End Infusion	19.4 ± 12.1 (n=17)	45.1 ± 19.3 (n=20)	59.6 ± 19.4 (n=15)

a. Data from NDA volume 1.46, ref. 6, table 14, shown as mean±SD in ng/ml.

Plasma tirofiban clearance rates

The next table shows the calculated tirofiban clearance for each of the three tirofiban dosing regimens. There was no significant difference between the three groups. The effect of age on tirofiban clearance was also examined and the results shown below. In contrast to the results from protocol #005, there was no significant difference in the clearance between the younger and older populations. There were very few women in the study, but no significant difference between the clearance of tirofiban by males and females was detected (despite a trend towards lower clearance in females).

Table 6.1.2.12.2d.2 Tirofiban clearance during protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin
Cl_s (ml/min)	264.1±102.6	201.7±67.8	233.3±101.6
Cl_s ≤65 yrs Cl_s >65 yrs	273.1 234.9	203.6 197.7	226.6 260.0
Cl_s Female (pooled) Cl_s Male (pooled)	179±23 (n=4) 263±95 (n=47)		

a. Data from NDA volume 1.46, ref. 6, table 15-16, shown as mean±SD in ng/ml.

The sponsor also attempted to discern the effect of heparin co-administration on the pharmacokinetics of tirofiban. To do this, the mean systemic clearances for tirofiban in protocols 004, 005 (no heparin) and 007 (heparin co-administration) were compared.

Table 6.1.2.12.2d.3 Tirofiban clearance during protocol #007, compared with #004 and #005[a].

Protocol	Mean Cl_s (95% CI)	Difference with #007	p-value
#004 (no heparin)	228.4 (172.9, 283.9)	-1.1 (-59.7, 57.4)	>0.25
#005 (no heparin)	167.7 (150.3, 185.2)	59.5 (32.7, 86.4)	<0.01
#007 (heparin)	227.3 (207.0, 247.4)		

Tirofiban elimination rates and half-life ($T_{1/2}$)

The next table shows the elimination rate constants along with the 95% confidence intervals, as well as the estimated half-life for tirofiban by treatment group. No significant differences between the groups were detected, There was also no significant effect of either gender or age on elimination rate (data not shown). Note that the estimated half-life in humans is significantly longer than that in the pre-clinical database for rats and dogs (see table 4.0.2.1).

Table 6.1.2.12.2d.4 Tirofiban elimination rate and half-life in protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin
Elimination rate (Hr^{-1})	0.314 (0.249, 0.378)	0.316 (0.288, 0.345)	0.332 (0.300, 0.365)
$t_{1/2}$ (hours)	2.2	2.2	2.1

a. Data from NDA volume 1.46, ref. 6, table 18.

The overall elimination rate of tirofiban in the presence of heparin (from protocol #007) was then compared with that from protocolOO4 (no heparin). No significant difference was detected.

Table 6.1.2.12.2d.5 Tirofiban elimination rates in #007 and 004"

Protocol	Mean Cl_s (95% CI)	Difference with #007	p-value
#004 (no heparin)	0.345 (0.270, 0.420)	-0.027 (-0.105, 0.051)	>0.25
#007 (heparin)	0.318 (0.293, 0.344)		

a. Data from NDA volume 1.46, ref. 6, table 19.

6.1.2.12.2d Primary Analyses of Protocol **#007** Trial Results

Pharmacokinetics/ Pharmacodynamics

Tirofiban volume of distribution(V_d)

The next table shows the V_d along with the 95% confidence intervals for tirofiban by treatment group. The V_d appeared to be highest in the lowest-dose treatment group. No effect of heparin could be estimated, as V_d was not measured in protocols #004 and #005.

Table 6.1.2.12.2d.4 Tirofiban volume of distribution, V_d, in protocol #007[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin
V_d (liters)	35.3±2.4	21.7±1.3	23.1±1.4

a Data from NDA volume 1.46, ref. 6, table 20.

Inhibition of platelet aggregation (IPA)

The table below shows the median and 95% confidence interval (CI) for IPA (expressed as %) for each of the treatment groups at 5 minutes and 2 hours after the start of the tirofiban bolus, at the end of the tirofiban maintenance infusion, and at 0.5, 1.5, 4, and 8 hours after the end of the tirofiban maintenance infusion. Both the 0.1 and the 0.15 µg/kg/min infusion protocols caused a >90% IPA at all time points during the infusion. Note how rapidly the median IPA declines following discontinuation of the tirofiban bolus.

Table 6.1.2.12.2d.5 Median IPA (%) values from protocol #007[a].

Time of infusion mins (range)	Tirofiban 5/0.5 +Heparin	Tirofiban 1010.1 +Heparin	Tirofiban 10/0.15 +Heparin	Pooled Heparin
Bolus (5 mins)	**72.5*** (57.5, 79.5)	**92.9*** (87.6, 95.5)	**95.5*** (83.9, 96.9)	-2.0 (-7.3, 5.1)
2 hours	47.1" (40.5, 70.1)	94.3 * (83.6, 96.3)	**100.0*** (95.6, 100.0)	-3.4 (-13.1, 10.3)
End infusion	**57.1*** (46.5, 72.6)	**90.9*** (79.4, 94.6)	**94.6*** (87.4, 97.3)	2.5 (-10.6, 16.8)
0.5 hrs post-infusion	**47.4*** (34.3, 58.8)	**79.9*** (66.0, 86.7)	**92.8*** (76.7, 96.4)	5.1 (-7.2, 11.8)
1.5 hrs post-infusion	28.6" (15.9, 46.2)	**50.4*** (44.2, 64.8)	**79.0*** (56.1, 86.8)	**3.7** (-8.3, 9.0)
4 hrs post-infusion	15.7 (7.5, 31.3)	**26.9*** (15.6, 41.6)	**46.8*** (24.1, 58.0)	-5.9 (-11.9, 3.7)
8 hrs post-infusion	12.0 (1.8, 16.7)	2.3 (-3.0, 19.4)	13.5 (2.4, 19.4)	-7.6 (-22.1, 3.3)

a. Data from NDA volume 1.46, ref. 4, table 21

b. * values differ from pooled heparin value <0.05. There was no significant difference between the three tirofiban groups

The % of subjects achieving ≥70% IPA at all points during the administration of study drug was also examined. As the table shows below, the higher dose regimens lead to significant inhibition in a large % of subjects.

Tab 6.1.2.12.2d.6 % of subjects achieving ≥70% IPA from protocol #007[a].

Time of infusion mins (range)	Tirofiban 510.5 +Heparin	Tirofiban 1010.1 +Heparin	Tirofiban 1010.15 +Heparin
Bolus (5 mins)	53.4 (24.7, 82.1)	91.1 (66.5, 100.0)	81.4 (53.3, 100.0)
2 hours	39.7 (9.6, 69.8)	85.1 (60.1, 100.0)	92.5 (63.8, 100.0)
End infusion	36.7 (6.6, 66.8)	83.3 (54.6, 100.0)	89.3 (55.5, 100.0)
0.5 hrs post-infusion	18.0 (0.0, 48.9)	62.5 (35.6, 89.4)	81.8 (48.0, 100.0)
1.5 hrs post-infusion	7.6 (0.0, 37.7)	22.9 (0.0, 49.3)	66.8 (35.0, 97.8)
4 hrs post-infusion	**3.3** (0.0, 33.4)	**3.5** (0.0, 30.4)	10.6 (0.0, 42.4)
8 hrs post-infusion	0	2.6 (0.0, 28.5)	0

a. Data from NDA volume 1.46, ref. 6, table 22.

6.1.2.12.2d Primary Analyses of Protocol **#007** Trial Results
Pharmacokinetics/ Pharmacodynamics(cont)

There was a higher % of subjects in the highest dose group who achieved 100% IPA during the trial, as shown below.

Table 6.1.2.12.2d.7 % of subjects achieving 100% IPA from protocol #007[a].

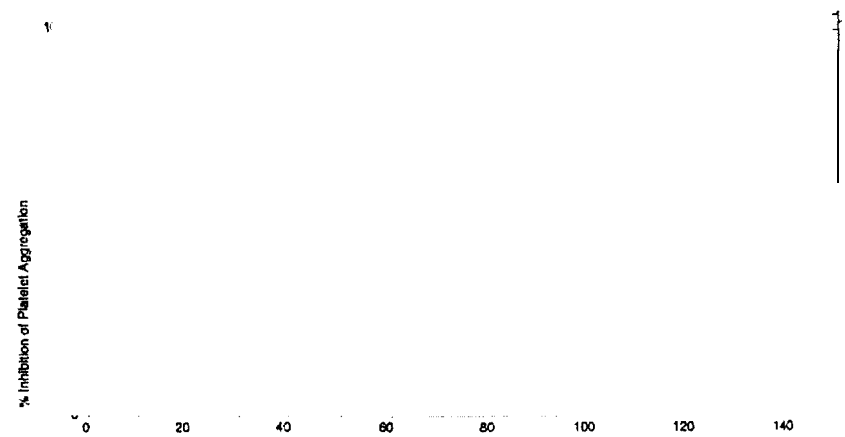
Time of infusion	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin
Bolus (5 mins)	0	3.4	31.8
2 hours	0	14.3	52.4
End infusion	5.3	14.3	26.7
0.5 hrs post-infusion	0	8.3	26.7
1.5 hrs post-infusion	0	4.0	5.9
4 hrs post-infusion	0	4.2	5.9
8 hrs post-infusion	0	0	0

a. Data from NDA volume 1.46, ref. 6, table 23, and electronic datasets.

Relationship of plasma concentration to IPA

As was done in protocol #005. the sponsor attempted to correlate the IPA data with tirofiban plasma concentration. Based on data shown in the graph provided by the sponsor below, the estimate for the C_{50} for tirofiban was 10.3 ng/ml (SE ±1.42, CI 7.5 to 13.1). This compares with the estimate of 15.5 ng/ml in protocol #005. While numerically lower, the sponsor felt that populational differences preclude any inferences about the potential effect of heparin on the tirofiban effects on IPA. This lower C_{50} would also be achieved more readily in all of the dosing groups (see table 6.1.2.12.2d. 1 above for tirofiban plasma concentrations).

Figure 6.1.2.12.2d. 1 Graphs of IPA vs. Tirofiban plasma concentration from protocol #007.



MK-0383 Concentration (μg/mL)

MK(5/0.05) Patients (□)
MK(10/0.10) Patients (0)
MK(10/0.15) Patients (Δ)
Solid line is fitted curve to Sigmoid-E_{max} model

Template bleeding times

Bleeding times were next compared between the tirofiban groups and heparin at the end of 2 hours. This is to be compared with protocol #005, where template bleeding times were measured after 24 and 48 hours. Bleeding times were consistently prolonged in the tirofiban group, relative to the heparin group. No statistical comparisons between the groups were performed.

Table 6.1.2.12.2d.8 Median template bleeding times from protocol #007[a].

Time of infusion	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Pooled Heparin
Baseline	5.5	5.0	6.2	5.2
2 hours	20.0	30.0	30.0	11.0

a. Data from NDA volume 1.46, ref. 6, table 24.

6.1.2.12.2d Primary Analyses of Protocol **#007** Trial Results
Pharmacokinetics/ Pharmacodynamics

The bleeding times were also prolonged over baseline in the tirofiban groups. The table below shows the fold-change in bleeding time (Bleeding time extension, BTE) data when compared with baseline values. Both of the high-dose groups had a numerically greater BTE than either the low-dose tirofiban or the pooled heparin groups.

Table 6.1.2.12.2d.9 Bleeding times extension (BTE) data from protocol #007[a].

Time of infusion	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Pooled Heparin
2 hours	3.0	4.9	4.7	2.1

a. Data from NDA volume 1.46, ref. 6, table 25.

Significantly, however, several subjects in the tirofiban groups had bleeding times 230 minutes (the longest period measured before the test was stopped), particularly in the two highest dose groups. No subject in the heparin group had a similar prolongation of bleeding time.

Table 6.1.2.12.2d.10 Subjects with bleeding times ≥30 minutes from protocol #007[a].

Time of infusion	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Pooled Heparin
Baseline	1/21 (5%)	0/29 (0%)	0/22 (0%)	0/20 (0%)
2 hours	5/19 (26%)	15/28 (54%)	13/21 (62%)	1/18 (6%)

a. Data from NDA volume 1.46, ref. 6, table 26.
b. * values differ from pooled heparin value <0.05. There were no significant differences between the three tirofiban groups.

Comparison of tirofiban effects with and without heparin

Finally, the sponsor compared the bleeding times in protocols #005 and #007. It should be noted that the IPAs for both protocols were similar (see table below). However, the average bleeding time was numerically longer in the current protocol, where heparin was used along with tirofiban. It is also important to note that the bleeding times were measured at very different time points during the infusion: protocol #005 at 24 hours; protocol #007 at 2 hours of infusion. No statistical comparisons have been performed.

Table 6.1.2.12.2d.11 Comparison of %IPA and bleeding times from protocols #005 and #007[a].

Infusion Tirofiban Dose	%IPA		Bleeding Time (mins)	
0.10 µg/kg/min	Protocol #005 82.9% (59.5, 89.4)	Protocol #007 90.9% (79.4, 94.6)	Protocol #005 9.8 mins (8.8, 13.3)	Protocol #007 30.0 mins (22.0, 30.0)
0.15 µg/kg/min	93.6 (87.9, 96.3)	94.6 (87.4, 97.3)	19.8 mins (14.8, 24.5)	30.0 mins (25.0, 30.0)

a. Data from NDA volume 1.46, ref. 6, table 27.

6.1.2.12.2d Primary Analyses of Protocol #007 Trial Results

Clinical **Cardiac Events**

There were no deaths, MIs, or emergency CABG procedures performed during the trial. The rate of repeat catheterization was quite low as well. The table below shows the incidences of repeat catheterization and repeat PTCA are shown below.

Table 1.2.12.2d.12 Cardiac procedures in protocol #007[a] prior to discharge.

Clinical event	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Tirofiban 10/0.15 +Heparin	Pooled Heparin
Infusion Period				
Recatheterization	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repeat revascularization/ PTCA	1 (5%)	0 (0%)	1 (4%)	1 (5%)
Hospital Discharge				
Recatheterization	1 (5%)	1 (3%)	0 (0%)	0 (0%)
Repeat revascularization	1 (5%)	1 (3%)	1 (4%)	1 (5%)

a Data from NDA volume 1.46, ref. 6, table 28, and electronic datasets.

6.1.2.13 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 number of subjects with any SAE and subject discontinuations due to AEs were both highest in the tirofiban 0.6/0/15 group (highest dose group). Drug-related AEs were higher in all three tirofiban groups than in the pooled heparin group.

Table 6.1.2.13.1 Clinical adverse experience (AE) summary from protocol #007[a].

Clinical event shown as # of subjects (% of total)	Tirofiban (5/0.5) n=21	Tirofiban (10/0.1) n=-30	Tirofiban (10/0.15) n=22	Pooled Heparin n=20
With Any AE	19 (90)	28 (93)	21 (95)	18 (90)
Without Any AE	2 (10)	2 (7)	1 (5)	2 (10)
With Serious AE	0 (0)	1 (3)	3 (14)	2 (10)
With Drug-Related AE[b]	12 (57)	16 (53)	14 (64)	7 (35)
With Serious and Drug-Related AEs	0 (0)	1 (3)	1 (5)	0 (0)
Discontinued due to an AE	1 (5)	0 (0)	6 (27)[c]	1 (5)
Discontinued due to Lab AE	0 (0)	0 (0)	3 (14)[d]	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

a. Data from NDA volume 1.46, ref. 6, table 29, and electronic datasets.

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

c. One subject, AN 242, experienced both clinical and lab AEs which led to discontinuation. Subject was included both here and in lab AEs.

d. Two subjects, AN 221 and 241, had both clinical and lab AEs which led to discontinuation. Subject was included both here and in lab AEs.

6.1.2.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

6.1.2.13.2 Comments on Specific Safety Parameters

Deaths

There were no subject deaths.

Serious Adverse Events

There were 6 serious adverse events. There were 3 bleeding-related SAEs in the tirofiban +heparin groups (subjects 1, 2, and 3), and one in the heparin group (subject 5). The subject narratives for these events are included below.

Tirofiban1 O/O.1+Heparin

1. AN 103-Postoperative Bleeding (Groin), Pancreatitis/LFT abnormalities, and Vasovagal Reaction: A 67-year-old female with unstable angina, non-Q wave myocardial infarction, sinus bradycardia, lst-degree AV block, status post PTCA and status post left carotid endarterectomy was randomized to MK(10/0.10) + heparin. The patient then had a successful atherectomy followed by PTCA of the proximal right coronary artery (RCA). "Significant back discomfort" during the procedure was noted. Following the procedure, the patient had back discomfort but no chest pain. Groin oozing at the catheter site was noted. There were three episodes of transient vasovagal reactions (lightheadedness, dizziness and hypotension), but these were easily corrected with IV fluids. A CT-scan was performed to rule out bleeding and showed no evidence of retroperitoneal hemorrhage, although the findings were suggestive of pancreatitis. The serum amylase was normal. Liver function tests were elevated at baseline, continued to increase throughout the study drug infusion, but normalized by hospital discharge. The investigator felt that these experiences prolonged hospitalization and that the bleeding at the right groin was possibly related to study therapy but that the vasovagal reaction was not related to study drug therapy.

Tirofiban 1010.15 +Heparin

2. AN 210–Coronary Artery Dissection: A 57-year-old male with a coronary stent, a history of a previous myocardial infarction, hypertension, hypercholesterolemia, who was experiencing nausea, vomiting, emesis, restlessness, back pain, and GI upset was admitted. An angiogram revealed a 90% proximal RCA lesion. The patient was randomized to MK(10/0.15) + heparin. The patient underwent a PTCA of the RCA. A moderate dissection developed and a stent was placed without complications, for the dissection and threatened closure of the RCA. The study therapy was discontinued. The patient was hospitalized until adequately anticoagulated, which prolonged his hospitalization. The patient recovered and was discharged.

3. AN 241–Retroperitoneal Hematoma: A 59-year-old female patient was admitted with an acute MI, bronchospasm, bronchitis and anxiety. A cardiac catheterization revealed 99% stenosis of her circumflex artery. The patient was randomized to therapy with MK(10/0. 15) + heparin. The PTCA was successful but required several catheter exchanges. The patient complained of abdominal pain in the right and left lower quadrants, in addition to new right femoral pain. Study therapy was discontinued. A new expanding femoral hematoma was found at the sheath site. An abdominal CT scan confirmed a small retroperitoneal bleed and a right femoral hematoma. Anticoagulants were discontinued and the bleeding stabilized. The patient was discharged. The investigator felt that the bleeds were both procedure related, but that study drug therapy or heparin could have contributed to the bleeding.

Of note, this subject also had an extremely elevated plasma level of tirofiban (335 ng/ml at the end of the infusion). The subject had normal renal function, but may have been dehydrated (BUN/crt 17/0.7), but had markedly abnormal LFTs (AST 24X upper limits of normal).

4. AN 242-Angina Pectoris: A 55-year-old male with hypertension, normal left ventricular function and RCA disease and prior PTCA procedures (3 months and 7 months) of the RCA, with good results, was readmitted for unstable angina. A cardiac catheterization confirmed a 95% RCA lesion with progression of a 70% stenosis in the proximal and mid circumflex arteries. The patient was randomized to therapy with MK(10/0.15) + heparin. The patient developed thrombocytopenia (70,000/mm 3) and heparin was discontinued. Platelet counts rose prior to discontinuation of the MK-0383; however, the platelet counts normalized only after both heparin and MK-0383 were stopped. The thrombocytopenia had no clinical consequence and did not delay hospital discharge. However, the thrombocytopenia (a non-serious adverse experience) was considered to be possibly drug related. Three days after discharge, the patient developed recurrent exertional angina (of moderate intensity) and was re-hospitalized to evaluate whether he had experienced acute closure of the RCA. A repeat cath revealed a 20% narrowing of the RCA without evidence of restenosis. The patient tolerated heparin therapy (4000 U bolus and 1000 U/ hour) during the catheterization without recurrence of the thrombocytopenia. The patient recovered and was discharged. In the opinion of the investigator, the readmission was not related to therapy with study medication.

6.1.2.13.2 Comments on Specific Safety Parameters (cont)

Heparin

5. AN 017-Postoperative Bleeding (Groin): A 67-year-old female with hypertension, ischemic heart disease, glaucoma, hypercholesterolemia, gout and spastic leg jerking related to anxiety entered this study. The patient was given heparin 10,000 U and was randomized to placebo + heparin. Prior to balloon inflation, the patient developed spastic jerking of her legs. Her leg jerking continued and the angioplasty procedure was abandoned. Two days later the patient felt a "pop" while walking and developed internal bleeding (classified as moderate) in the groin at the catheter site. Two units of blood were given and bypass surgery was postponed for an additional day. The patient subsequently underwent a triple bypass and the recovery was uneventful. The investigator felt the patient's experience was not related to study drug therapy or heparin.

6. AN 112–Unstable Angina Pectoris: A 56-year-old female with chest pain, diabetes mellitus, hypertension, hyperlipidemia, hypokalemia, anxiety, nausea, back pain, congestion, gout, arthritis and anemia entered the study. The patient was randomized to placebo + heparin, and underwent a successful PTCA of the proximal left anterior descending (LAD) and diagonal arteries. The patient did very well and was discharged. Approximately 4 days later, the patient developed progressive angina and was readmitted. A positive thallium stress test showed a reversible defect in the inferior wall. A myocardial infarction was ruled out by serial enzymes. Recatheterization revealed a patent LAD but stenosis of the left circumflex artery (LCA). The patient underwent PTCA of the LCA with good results and was discharged. The investigator felt that the patient's experience was not related to the study therapy.

Bleeding Adverse Events

Bleeding AEs will be discussed in details in sections 8.1 and 8.2. The table below summarizes the bleeding AEs in protocol #007 by site of bleeding. There was a slightly higher % of subjects with bleeding AEs in the highest dose tirofiban + heparin group, when compared with heparin. The high dose tirofiban +heparin group also had more oropharyngeal bleeding and hemoptysis.

Table 6.1.2.12.2d.12 Bleeding AEs in protocol #007[a] prior to discharge.

Clinical event	Tirofiban (5/0.5) n=21	Tirofiban (10/0.1) n=30	Tirofiban (10/0.15) n=22	Pooled Heparin n=20
With Clinical Bleeding Events	15 (71)	22 (73)	19 (86)	12 (60)
Without Clinical Bleeding Events	6 (29)	8 (27)	3 (14)	8 (40)
Catheter Site	14 (67)	19 (63)	14 (64)	10 (50)
Genitourinary/Hematuria	6 (29)	8 (27)	8 (36)	6 (30)
IV Site	1 (5)	1 (3)	1 (5)	0 (0)
GI	1 (5)	1 (3)	1 (5)	1 (5)
Oropharyngeal	0 (0)	0 (0)	3 (14)	1 (5)
Hemoptysis	0 (0)	0 (0)	3 (14)	0 (0)
Retroperitoneaf	0 (0)	0 (0)	1 (5)	0 (0)
Other	2 (10)	1 (3)	1 (5)	a

a. Data from NDA volume 1.46, ref. 6, table 28, and electronic datasets.

One subject, AN 165, in the tirofiban 10/0.1 +heparin group, met the criteria for 'major bleed.'

Two subjects required transfusions: AN 017 in the heparin only group; and AN 241 in the tirofiban 10/0.1 +heparin group.

6.1.2.14 Protocol #007 Efficacy Summary

This study was designed to assess the pharmacokinetics of tirofiban in subjects with UAP/NQWMI, and to compare the effect of tirofiban on coagulation parameters with that of heparin.

pharmacokinetics

The clearance of tirofiban was similar in all three doses examined in the protocol. In contrast with the results from protocol #005, age of the subject did not affect clearance of tirofiban (see table 6.1.2.12.2d.2).

In the subjects in the two highest dose regimens of tirofiban , the bolus and infusion of tirofiban achieved high plasma concentrations of tirofiban within 30 minutes (see table 6.1.2.12.2d. 1). No information about the plasma levels between 30 minutes and 24 hours are available. The plasma levels were stable at 24 and 48 hours in all tirotiban groups.

The estimated $T_{1/2}$ for tirofiban in humans (2.1-2-2 hours) is longer than reported for rats and dogs (24-40 minutes).

Pharmacodynamics

The two higher doses of tirofiban used in the protocol cause a >70% inhibition of platelet aggregation in almost all subjects, and had a significantly greater effect than did heparin. The lowest dose of tirofiban was less consistent effective in inhibiting platelet aggregation, (see table 6.1.2.12.2d.5). There is also a suggestion that the two highest dose groups had a greater effect to prolong bleeding time at the end of 2 hours (see table 6.1.2.12.2d.8).

The calculated C_{50} for IPA was lower in this trial than in protocol #005, but diierences between the two trials makes strict comparison of these results difficult.

Clinical endpoints

No inferences as to the efficacy of tirofiban can be drawn from the small numbers of clinical events. The population enrolled in the trial underwent cardiac procedures, including angiography, PTCA and CABG

6.1.2.15 Protocol #007 Safety Summary

The small number of subjects makes overall assessment of safety difficult. There were no unexpected toxicities detected.

The most common bleeding AEs related to catheter-site bleeding. No large difference in the incidence of this AE was detected between the groups, although the tirofiban groups as a whole had a higher frequency of them than the heparin alone group [see table 6.1.2.12.2d. 12). Non-catheter-site bleeding was increased in the highest dose group of tirofiban +heparin. In particular, oropharyngeal bleeding and hemoptysis were increased (see table 6.1.2.12.2d. 12).

6.1.2.16 Protocol #007 Reviewer's Conclusions

1. Systemic clearance of tirofiban is independent of rhe doses used in this study, and was not dependent on either sex or gender.

2. Tirofiban produces a >70% inhibition of ADP-induced platelet aggregation (IPA) in a high percentage of subjects at the two higher dosing regimens used (tirofiban 10/0. 1 and 10/0. 15).

3. There was an increased incidence of oropharyngeal bleeding and hemoptysis in the highest dose tirofiban +heparin group (10/0. 15). These AEs will be integrated into the larger combined safety database in section 8.1.

6.1.3 Review of Protocol #008

6.1.3.1 Title of Study

A Randomized, Double-Blind Study of MK-0383 in Patients With Unstable Angina Pectoris Concomitantly Receiving Heparin (Protocol #008).

6.1.3.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 1.37, Table A-l @ages A-6 to A-101).

Protocol #008 trial was conducted at 5 sites in the United States.

6.1.3.3 Background

Initial protocol submitted: 9.22.93

First protocol amendment submitted: 3.4.94

This amendment added a second panel of subjects to the protocol, who received tirofiban at a dose of 0.6 µg/kg/min for 30 minutes, followed by an infusion of 0.15 µg/kg/min for the remainder of the 48 hours.

Subject entry: 11.93 to 7.94

Case report form cutoff: 10.10.94

6.1.3.4 Study Design

In this randomized, double-blind study, patients with unstable UAPMQWMI concomitantly receiving heparin was designed to:

1) investigate the safety, tolerability and effects of tirofiban on subsequent cardiac events when used in patients with unstable angina (UAP)/non-Q-wave myocardial infarction (NQWMI) concomitantly receiving heparin.

2) study the phatmacolcmetics and pharmacodynamics of tirofiban on a background of ASA and heparin;

3) investigate the incidence of adverse cardiac events (recurrent cardiac ischemia, refractory angina pectoris, myocardial infarction, and need for coronary revascularization) during infusion of study drugs (tirofiban + heparin versus heparin), and during subsequent hospitalization.

Subjects were studied in two panels (24 patients/panel). All patients received concomitant aspirin. Within each panel, patients were randomized to receive either tirofiban or matching placebo (3:1 ratio); 18 patients were to receive tirofiban and 6 patients matching placebo. Patients were given study drug for 48 hours and followed through hospital discharge for clinical events. In contrast with protocol #007, this study did not require that the subjects undergo PTCA.

6.1.3.5 Primary and Secondary Endpoints

The primary aim of the study was to collect pharmacokinetic and pharmacodynamic data, including:

1) Serial tirofiban serum concentrations;
2) Serial measurements of the % inhibition of ADP-induced aggregation; and
3) Serial measurements of the extension of bleeding times.

While not powered to detect differences in clinical endpoints, the study did collect information about the following clinical events:

1) Ischemic episodes;
2) Refractory angina pectoris;
3) Myocardial infarction;
4) Need for urgent cardiac revascularization; and
5) Death.

6.1.3.6 Number of subjects/ randomization

Table 6.1.3.6.1 Summary of subjects entered into each dose group in protocol #008[a].

	Tirofiban 0.4/0.1[b] +Heparin	Tirofiban 0.6/0.15 +Heparin	Placebo +Heparin
Entered	2 1	15	12

a. Data from NDA volume 1.47, reference 7, page 6132.

b. During this review, the first number stands for the bolus, in µg/kg/min for 30 minutes, and the second number for the infusion, in µg/kg/min over the remainder of the infusion period.

6.1.3.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

The study population consisted of patients of either sex who presented to the hospital with myocardial ischemic pain caused by either unstable angina or non-Q-wave myocardial infarction, defmed as one of the following:

1) Accelerating pattern of angina1 pain (episodes of angina that are more frequent, severe, longer in duration and/or precipitated by less exertion) with electrocardiographic evidence of myocardial ischemia, defmed as follows:

a) persistent or transient ST-segment depression 20.1 mV (0.08 seconds after the J-point) in two contiguous leads, or

b) persistent or transient T-wave inversion in two contiguous leads, or

c) transient (<20 min) ST-segment elevation 20.1 mV in two contiguous leads.,

2) Recent onset of chest pain (<4 weeks) which is suggestive of myocardial ischemia, U 5 minutes but not longer than 1 hour in duration, and occurring at rest or with minimal effort.

3) Angina pectoris occurring at rest, or frequently (greater than or equal to two episodes/day) with modest activity, during the 2 weeks prior to study enrollment.

It was expected that a certain number of patients who presented with chest pain and ST-segment deviation or T-wave inversion would have creatine kinase (CPK) elevations consistent with a non-Q-wave myocardial infarction. Evidence of non-Q-wave infarction did not exclude the patient from the study. Patients must:

1) Have had their most recent episode of chest pain within 48 hours preceding the time of randomization.

2) Have had clinical evidence of underlying coronary artery disease by having one of the following:

a) Electrocardiographic evidence of myocardial ischemia during an episode of chest pain.

b) Prior history of myocardial infarction, positive exercise stress test or dipyridamole (or adenosine) nuclear stress test, or 250% luminal diameter narrowing of a major coronary artery on a prior coronary arteriogram.

c) Typical exertional chest pain relieved by rest or nitroglycerin, or both.

3) Be ≥18 and ≤80 years of age.

Exclusion Criteria

1) Pregnant or nursing women and women of childbearing potential.

2) Presence of new pathologic Q-waves (>0.03 seconds in duration) or ST-segment elevation 20.1 mV in two contiguous leads persisting for ≥20 minutes, suggestive of evolving acute Q-wave myocardial infarction.

3) Coronary angioplasty within 6 months or coronary bypass surgery within 3 months prior to study start.

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

5) Patients with uncontrolled severe cardiac arrhythmias, including persistent sinus tachycardia >120 beats/min.

6) Patients receiving oral anticoagulant medications (i.e., warfarin) within 1 week prior to enrollment or antiplatelet agents (except aspirin) which have been ingested within 24 hours of enrollment (such as nonsteroidal anti-inflammatory drugs, dipyridamole, and sulfmpyrazone). Patients receiving ticlopidine within 7 days of study enrollment were not eligible for randomization.

7) a) Heparin allergy or intolerance (including heparin-induced thrombocytopenia).

b) Aspirin allergy or intolerance.

8) Thrombolytic therapy within 3 weeks prior to enrollment, or documented myocardial infarction within 3 weeks prior to the most recent episode of chest pain.

6.1.3.7 Inclusion/ **Exclusion** Criteria **(cont)**

Exclusion Criteria

9) Contraindications to anticoagulation:

a) Past or present bleeding disorder including a history of gastrointestinal bleeding or presence of occult blood in the stool. Any patient with a known platelet disorder, history of thrombocytopenia, or previous exposure to fibrinogen receptor antagonist was also 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 cerebrovascular disease, including transient ischemic attacks.

d) Prolonged cardiopulmonary resuscitation with 1 minute or more of external cardiac massage within the 2 weeks prior to study enrollment.

e) Severe trauma within 6 months prior to study enrollment.

f) Major surgical procedure within 3 months of study enrollment.

g) Active peptic ulcer disease within 6 months prior to study enrollment.

h) Invasive procedure (or lithotripsy) within 14 days of study enrollment that would significantly increase the risk of hemorrhage, such as biopsy, or arterial puncture.

i) Probable pericarditis.

j) Presence of significant retinopathy (i.e., hemorrhages or exudates).

10) Angina precipitated by obvious provoking factors (e.g., arrhythmia, severe anemia, hypotension, or hyperthyroidism).

11) Left bundle branch block.

12) Pre-excitation syndrome, e.g., Wolff-Parkinson-White syndrome.

13) History of recent or ongoing alcohol abuse or parenteral or other drug abuse.

14) Patients with acute pulmonary edema (rales present over more than 50% of the lung fields) or patients with severe congestive heart failure (New York Heart Association Functional Class III or IV).

15) Patients with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.

16) Patients with uncontrolled diabetes mellitus or other uncontrolled endocrinopathy.

1'7) Patients with clinically significant systemic renal, pulmonary, hepatic, neurological, or hematological disorders.

18) Patients with clinically significant abnormal laboratory findings including:

a) Serum creatinine >1.6 mg/dL (>140 mmol/L).

b) Hemoglobin <12 gm/dL (120 g/L) *or* hematocrit <36%.

c) Platelet count <150,000/mm^3 (<150 x 10^9 /L).

d) Prothrombin time or activated partial thromboplastin time (aPTT) >1.2X laboratory control.

19) Sustained supine, sitting, or standing systolic blood pressure <90 mmHg.

20) Patients receiving another investigational drug within 4 weeks prior to the study.

21) Patients with any other medical condition that, in the investigator's opinion, makes 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 patient.

22) Inability to give informed consent.

6.1.3.8 Dosage/ Administration

Two-dose regimens were studied in two sequential panels. These two-dose levels were chosen to allow direct comparisons between this study and a previous double-blind study in the same patient population in which tirofiban was administered in the absence of concomitant heparin (protocol 005). Protocol 005 had three panels patients with UAP/NQWMI who *were* given tirofiban or heparin infusion for 48 hours (see section 6.1.1.1 for review). The two highest dosing regimens from the earlier study were chosen for the current study of tirofiban administered in combination with heparin. The first consisted of a 30-minute loading infusion of 0.4 mg/kg/min followed by a 47.5-hour maintenance infusion of 0. I mg/kg/min (tirofiban 0.4/0. 1); the second had a loading infusion of 0.6 mg/kg/min followed by a maintenance infusion of 0.15 mg/kg/min (tirofiban 0.6/0. 15). These two regimens were thus used to characterize the pharmacokinetic and pharmacodynamic effects of the presence of heparin on tirofiban as well as the safety profile of this combination therapy.

All patients also received concomitant aspirin if tolerated.

6.1.3.9 Duration/ Adjustment of Therapy

Study drug was infused for a total of 48 hours.

Study drug was discontinued for clinically relevant hemorrhage, a significant decrease (>3.0 g/dL) in blood hemoglobin, need for transfusion of ≥2 units or corrective surgery, or significant thrombocytopenia. If at any time the platelet count dropped to 100,000/mm^3 or decreased to 60% of the pre-drug value, the test was repeated immediately. If the platelet count decreased to <90,000/mm^3 the infusion of study drug and heparin was discontinued. In addition, study drug was to be discontinued for any of the following reasons:

1) A condition that necessitated thrombolytic therapy, including acute closure during PTCA or atherectomy.
2) Need for emergent coronary artery bypass surgery, repeat angioplasty, atherectomy, or stent placement.
3) Need for intra-aortic balloon counter pulsation or percutaneous bypass.

6.1.3.10 Safety and Efficacy Endpoint Measured

Table 6.2.3.10. Timetable or clinical observations and lab measurements in protocol #008[a].

	Start Infusion							Stop Infusion	
	0	0.5 hrs	2 hrs	6 hrs	12 hrs	24 hrs	36 hrs	48 hrs	60 hrs
History	X								
Physical	X					X		X	
CXR	X								
ECG	X			X	X	X		X	
Plasma tirofiban	X	X				X	X	X	X
ADP-induced platelet aggregation	X	X				X	X	X	X
Bleeding time	X					X		X	
PT/PTT	X			X		X		X	X
Complete labs[d]	X					X		X	
CPK MB	X			X	X	X	X	X	X
Hgb/Hct/Plt #	X	X	X	X	X	X	X	X	X
Urine crt	X					X			
Urine tirofiban						X			
Serum crt						X			
Drug Infusion									

a. Data from NDA volume 1.47, reference 7, table 2.

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

c. Heparin dosed per protocol-specified guidelines. Heparin was to be D/C'd if possible immediately after the procedure.

d. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis) and (4) Stool for occult blood (as available).

6.1.3.11 Statistical Considerations

The safety and efficacy analyses were based on the intention-to-treat principle, with one exception: patients 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 patients 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 patient 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 patient randomization). Acute coronary ischemic syndrome was defmed as one of the following:

(1) Unstable angina, as defmed by an episode of typical angina1 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

6.1.3.11 Statistical Considerations (cont)

(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 ≥85 years of age (Inclusion Criterion 3). Since only 1 patient was known to have a last episode of chest pain more than 72 hours before his PTCA/ atherectomy procedure and none of the patients was more than 85 years old, the per-protocol analyses as described would have been redundant. One patient (AN 5676) received study drug, but did not have a qualifying procedure. In order to include this patient 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 for analysis of the composite endpoints only.

2) Analytical Methods

The primary hypotheses in protocol 008 were:

1. The first hypothesis is that 'MK-0383 (tirofiban) will be safe and well tolerated in patients with UAP/NQWMI' receiving: 0.4 mg/kg/min over 30 minutes and then a maintenance infusion of 0.10 mg/kg/min for 47.5 hours in Panel 1 of the study, and 0.6 mg/kg/min over 30 minutes and then a maintenance infusion of 0.15 mg/kg/min for 47.5 hours in Panel 2 of the study.

Based on the actual sample size, the sponsor calculated that if none of the subjects receiving tirofiban suffered a particular adverse event, such as thrombocytopenia or major bleeding event, it can be assumed with 90% confidence that the true rate for the adverse event among all patients receiving the same dosing regimen of tirofiban is either 10% (for panel 1) or 14% for panel 2.

The incidence of a major bleeding event in unstable angina patients on heparin was expected to be between 3% and 5%. Assuming that the incidence in UAP patients on heparin and tirofiban is likewise 3%, there is only a 1.6% chance that more than 2 subjects would experience a major bleeding event. With an incidence rate of 5% there is a 6% chance that more than 2 subjects would experience a major bleeding event. Thus three or more events will call the safety of tirofiban coadministration with heparin into question

2. The second hypothesis states that 'when administered with heparin, the plasma concentration of MK-0383 will *not* differ by more than 35% from that observed with MK-0383 alone in historic controls.'

Since plasma concentration is a function, in part, of weight (which determines infusion rate) it was felt that systemic plasma clearance of tirofiban would be a more appropriate pharmacokinetic comparator. Patients in the current trial received exactly the same doses of MK-0383 and aspirin as patients in protocol #005. The effect of heparin on the pharmacokinetics of tirofiban was explored by comparing this study with the results from Protocol 005.

3. A third objective of the study was to 'provide estimates of clinical ischemic event frequencies from time of initiation of study drug therapy to hospital discharge in patients with UAPMQWMI.' It is recognized that a study of this size will not provide adequate power to detect clinically meaningful differences between treatment groups with respect to clinical outcomes such as the incidence of ischemic episodes, refractory angina, or myocardial infarction.

Multiplicity

No multiplicity adjustments were stipulated by the protocol. No multiplicity adjustments were made and all tests were performed at the 5% level of significance.

Exploratory Analyses

The effect of age and renal function on the systemic plasma clearance of MK-0383 were studied.

Interim Analyses

No formal interim analyses were stipulated by the protocol and none were performed.

Statistical Analysis

1) Approaches to Analysis

The statistical analysis of pharmacokinetic and efficacy data followed a 'per-protocol' approach. Only patients who were currently on drug at the time window specified in the protocol were included in the analysis.
Missing measurement values were not estimated. All patients were included in the analysis of safety data. In the presentation of summary statistics for vital signs measurements, values for time points during infusion were included at that time point only if the patient was still being infused.

6.1.3.11 Statistical Considerations (cont)

2) Statistical Methods

Pharmacokinetics

Systemic plasma clearance of the drug was compared among the two tirofiban panels using an ANOVA model that included factors for dose, age, gender, and creatinine clearance as well as all two-way interactions. The relationship between creatinine clearance and age and between creatinine clearance and systemic plasma drug clearance was investigated using regression and Spearman's rank correlation. Analysis of variance was used to evaluate the effect ofheparin on systemic plasma drug clearance, by comparing the high- and low-dose groups in this study (tirofiban + heparin) with the corresponding dose groups in protocol 005 (tirofiban in the absence of heparin). Results from this analysis should be viewed with caution since they may contain bias due to potentially different patient populations and study conditions, nonrandomization, and other concerns inherent in comparing to a historical control.

Pharmacodynamics

An analysis of percent inhibition of platelet aggregation (IPA%) was completed on 5 mM ADP light transmission data. Primary efficacy endpoints included the IPA% at the end of the bolus infusion (0.5 hours) and at the end of the sustained infusion (48 hours). Because many subjects on tirofiban approached 100% inhibition of ADP-induced platelet aggregation, the data are not normally distributed. Therefore, medians instead of means and nonparametric methods were used to draw inference about platelet inhibition in the general patient population.

Pharmacodynamic Efficacy - Comparison of IPA with Plasma Concentration

Plasma concentrations for the two panels across all time points were plotted against the corresponding values of IPA for the respective time points. Pooled IPA (%) and tirofiban concentrations from patients in the two-dose panels were fit to a sigmoid E_{max} model to allow calculation of the C_{50} (the concentration that yields 50% IPA) and the Hill coefficient. The model assumed that E_{max} was 100% inhibition.

Pharmacodynamic Efficacy - Breeding Times

Another measure of drug efficacy in preventing platelet aggregation was template bleeding time. Bleeding time extension (BTE) was calculated by dividing each template bleeding time by the template bleeding time predose (-0.5 hours).

Clinical Cardiac Events

The incidence rates for clinical cardiac events (progression to myocardial infarction, urgent revascularization, and/or death) during study infusion and at hospital discharge were tabulated. All repeat catheterizations were also recorded.

Safety

Safety parameters included spontaneously reported adverse events and vital signs, which are summarized descriptively. Several important lab measurements including hematocrit, hemoglobin, and platelet count were also summarized. For safety analysis, statistical significance of the difference between groups was based on Fisher's exact test or Wilcoxon's rank test.

6.1.3.12 Efficacy Outcomes

6.1.3.12.1 Subject Demographics & Baseline Characteristics

The first table shows the summary of demographics and baseline characteristics for the trial.

Table 6.1.3.12.1.1 Demographics of the protocol #008[a].

Demographic n (%)	Tirofiban 0.4/0.1	Tirofiban 0.6/0.15	Pooled Heparin
Total Randomized	21	15	12
Gender n			
Male	14 (67)	13 (87)	9 (75)
Female	7 (33)	2 (13)	3 (25)
Race			
Caucasian	15 (71)	8 (53)	10 (83)
Black	6 (29)	6 (40)	1 (8)
Hispanic	0 (0)	1 (7)	1 (8)
Presentation			
Unstable Angina	20 (95)	1.5 (100)	11 (92)
Non-Q-Wave MI	1 (5)	0 (0)	1 (8)
Ischemic ECG changes	11 (52)	8 (53)	9 (75)
Mean Age (± SD)	56.2 (±10. I)	63.4 (±1 1.3)	62.9 (±I 1.4)
Age Range (Yrs)	39-75	39-79	42-77
Mean Weight, kg (± SD)	91.7 (±16.9)	89.5 (±21.9)	93.4 (±18.7)
Weight Range	61.7-133.5	60.8-130.3	70.8-120.8

a. Data from NDA volume 1.47, ref 7, table 4, based on all randomized subjects.

Table 6.1.3.12.1.2 Antecedent history of coronary artery disease in protocol #008[a].

Demographic n (%)	Tirofiban 5/0.5 +Heparin n=21	Tirofiban 10/0.1 +Heparin n=15	Pooled Heparin n=12
Angina Pectoris	16 (76)	12 (80)	7 (58)
Myocardial Infarction	14 (67)	5 (33)	8 (67)
Coronary Artery Bypass Grafting	5 (24)	4 (27)	2 (17)
Angioplasty	6 (29)	6 (40)	2 (17)

a. Data from NDA volume 1.47, reference 7, table 5.

6.1.3.12.2 Disposition of Subjects

More subjects were discontinued for clinical AEs in the tirofiban groups.

Table 6.1.3.12.2.1 Summary of subjects entered into each dose group in protocol #008[a].

	Tirofiban 5/0.5 +Heparin	Tirofiban 10/0.1 +Heparin	Pooled Heparin
Entered	21	15	12
Completed	14 (66%)	13 (86%)	9 (75%)
Discontinued: Total	4	4	1
Clinical AEs	1	2	0
Laboratory AEs	0	1	0
Other	3	2	1

a. Data from NDA volume 1.47, reference 7, table 9.

6.1.3.12.1 Subject Demographics & Baseline Characteristics

The reasons for discontinuation are listed below. Note that the only discontinuations for bleeding AEs occurred in the tirofiban groups (a total of 3 subject, 8% of all tirofiban subjects).

Table 6.1.: 2.2.2 Reasons for discontinuation in protocol #008[a].

Treatment Group	Patient #	Infusion Duration (hrs)	Reason for Discontinuation
Tirofiban (0.4/0.1)	AN 010	16.75	Bleeding AE
	AN 011	18	Ischemic Event
	AN 015	17	Ischemic Event
	AN 031	36	Protocol Deviation
	AN 094	43	Protocol Deviation
Tirofiban (0.6/0.15)	AN 099	26	Bleeding AE
	AN 101	12	Ischemic Event
	AN 106	39.6	Bleeding AE
Placebo	AN 102	40.5	Protocol Deviation

a. ata from NDA volume 1.47, ref. 7, table 10.

6.1.3.12.2a Subject Selection

No information is available about subject selection in protocol #008.

6.1.3.12.2b Protocol Violations & Deviations

Several individuals were not included in the IPA analysis due to discontinuation (see above) or for missing lab values. In addition to those subjects listed above, 4 subjects in the tirofiban 0.4/0.1 group had missing lab values.

6.1.3.12.2d Primary Analyses of Protocol #008

Pharmacokinetics/pharmacodynamics

plasma tirofiban concentrations

The first table shows the average plasma tirofiban levels during the trial. No values were drawn between 0.5 hrs and 24 hours.

Table 6. 3.12.2d.1 Plasma tirofiban concentrations during protocol #008[a].

Time of Infusion	Tirofiban 0.4/0.1 +Heparin n=19	Tirofiban 0.6/0.15 +Heparin n=14
0.5 hrs	54.2k23.7	83.6±32.0
24 hrs	50.4±16.2	85.8±25
36 hrs	49.3±13.5	88.9±28.2
48 hrs	48.6f18.7	92.4±31.3

a. Data fr NDA volume 1.47, ref. 6, table 12, shown as mean±SD in ng/ml.

Plasma tirofiban clearance rates

The next table shows the calculated tirofiban clearance for each of the two tirofiban dosing regimens. There was no significant difference between the two groups. The effect of age on tirofiban clearance was also examined and the results shown below. Older subjects had a significantly lower clearance of tirofiban than younger subjects (p=0.001). The sponsor was unable to determine whether this was due to a possible decrease in renal function in the elderly (renal clearance is a pivotal pathway for tirofiban clearance). There was no significant difference between the clearance of tirofiban by males and females detected.

6.1.3.12.2d Primary Analyses of Protocol #008

Pharmacokinetics/pharmacodynamics

Table 6.1.3.12.2d.2 Tirofiban clearance during protocol #008[a].

	Tirofiban 0.4/0.1 +Heparin n=19	Tirofiban 0.6/0.15 +Heparin n=14
Cl, (ml/min)	187.8 (n=19) (163, 212)	151.6 (n=14) (134, 169)
Cl, ≤65 yrs Cl, >65 yrs	193.1 (n=17) 143.2 (n=2)	167.5 (n=7) 135.6 (n=7)
Cl, Female (pooled) Cl, Male (pooled)	170.5 (n=8) 173.9 (n=25)	

a. Data from NDA volume 1.47, ref. 7, table 14.

The sponsor also attempted to discern the effect of heparin co-administration on the pharmacokinetics of tirofiban. To do this, the mean systemic clearances for tirofiban in protocols #005 (no heparin) and #008 (heparin co-administration) were compared. There was no significant differences between the two groups. The sponsor concluded that heparin did not affect the clearance of tirofiban in protocol #008.

Table 6.1.3.12.2d.3 Tirofiban clearance during protocol #008, compared with #005[a].

Protocol	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin
#005 (no heparin)	173.0	155.9
#008 (heparin)	187.8	151.6

a Data from NDA volume 1.47, ref. 7, page 6172.

Tirofiban elimination rates, half-life, and volume of distribution(V_d)

These were not calculated in this protocol.

inhibition of platelet aggregation (IPA)

Table 6.1.3.12.2d.4 shows the median and 95% confidence interval (CI) for IPA (expressed as %) for each of the treatment groups at 30 minutes, 24 and 48 hours after the start of the tirofiban bolus. While both dosing regimens of tirofiban had a significant effect on IPA compared with heparin, the high-dose tirofiban had a higher overall IPA at all three time-points.

Table 6.1.3.12.2d.5 Median IPA (%) values from protocol #008[a].

Time of infusion median (range)	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	Pooled Heparin
30 mins	86.3* (84, 96)	97.1* (94, 99)	-4.9 (-25, 2.4)
24 hours	82.1* (74, 87)	95.8* (95, 98)	-2.4 (-24, 1.7)
48 hours	89.1* (82, 93)	94.6* (88, 97)	-2.1 (-29, 3.3)

a. Data from NDA volume 1.46, ref. 7, table 15.

b. * values differ from pooled heparin value <0.05. There was no significant difference between the three tirofiban groups.

6.1.3.12.2d Primary Analyses of Protocol #008
Pharmacokinetics/pharmacodynamics (cont)

The percentage of subjects achieving ≥70% IPA at all points during the administration of study drug was also examined. Both doses achieved 270% IPA in a high percentage of subjects.

Table 6.1.3.12.2d.6 % of subjects achieving ≥70% IPA from protocol #008[a].

Time of infusion	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin
30 mins	100 (n=19)	93.3 (n=15)
24 hours	87.5 (n=16)	100 (n=14)
48 hours	92.9 (n=14)	100 (n=13)

a. Data from NDA volume 1.47, ref. 78, table 16.

Next, the sponsor compared the effectiveness of tirofiban in achieving 170% IPA in the presence of heparin (current protocol #008), and in the absence of heparin (#005). There was no significant difference detected.

Table 6.1.3.12.2d.7 Effectiveness of tirofiban in achieving ≥70% IPA in the presence and absence of heparid.

	Tirofiban regimen					
	Tirofiban 0.4/0.1			Tirofiban 0.6/0.15		
Infusion Time	0.5 hrs	24 hrs	48 hrs	0.5 hrs	24 hrs	48 hrs
With Heparin (#008)	86.3	82.1	89.1	97.1	95.8	94.6
Without Heparin (#005)	89.6	82.9	86.3	96.0	93.6	92.1

a. Data from protocols #008 and #005. Expressed as percentage of subjects who achieved ≥70% IPA at the listed time point.

Similar to what was done in protocol #005 and #007, the sponsor next fitted the plasma concentration-IPA data to a sigmoidal curve. The fitted C_{50} value of the pooled data was 12.2 ng/ml (±0.9 SE). The Hill coefficient was 1.25 (±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.

Template bleeding times

Bleeding times were next compared between the tirofiban groups and heparin at the end of 24 and 48 hours. This is to be compared with protocol #005, where template bleeding times were also measured after 24 and 48 hours. Bleeding times were consistently prolonged in the tirofiban group, relative to the heparin group. The high-dose tirofiban group also had a significantly greater effect on bleeding time than the low-dose group.

Table 6.1.3.12.2d.8 Median template bleeding times from protocol #008[a].

Time of infusion	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	Pooled Heparin
24 hours (mins)	14.0 (n=19)[b] (12.5, 22.0)	25.7 (n=14)[b,c] (15.7, 30.0)	6.5 (n=12) (4.8, 8.8)
48 hours	20.0 (n=17)[b] (13.0, 25.0)	30.0 (n-12)[b,c] (20.5, 30.0)	4.0 (n=11) (3.5, 7.5)

a. Data from NDA volume 1.47, ref. 8, table 18.
b. Differs significantly from heparin group (p<0.010).
c. Differs from low-dose tirofiban group (p<0.010).

6.1.3.12.2d Primary Analyses of Protocol #008
Pharmacokinetics/pharmacodynamics (cont)

The bleeding times were also prolonged over baseline in the tirofiban groups. The table below shows the fold-change in bleeding time (Bleeding time extension, BTE) data when compared with baseline values. Both of the tirofiban groups had a numerically greater BTE than the pooled heparin groups.

Table 6.1.3.12.2d.9 Bleeding times extension (BTE) data from protocol #008[a].

Time of infusion	Tirofiban 0.410.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	Pooled Heparin
24 hours	2.8	2.5	1.5
48 hours	2.9	4.4	0.8

a. Data from NDA volume 1.47, ref. 7, table 19.

Significantly, several subjects in the tirofiban groups had bleeding times 230 minutes (the longest period measured before the test was stopped). No subject in the heparin group had a similar prolongation of bleeding time, especially in the high-dose tirofiban group.

Table 6.1.3.12.2d.10 Subjects with bleeding times ≥30 minutes from protocol #008[a].

Time of infusion	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	Pooled Heparin
24 hours	5/19 (26%)	7/14 (50%)	0/12 (0%)
48 hours	5/17 (29%)	7/12 (58%)	0/11 (0%)

a. Data from NDA volume 1.47, ref. 7, table 20.

Comparison of tirofiban effects with and without heparin

Finally, the sponsor compared the bleeding times, the bleeding time extensions, and the % of subjects with bleeding times >30 minutes in protocols #005 and #008. It should be noted that the % of subjects achieving ≥70% IPA was similar for both protocols (see table 6.1.3.12.2d.7 above). However, the average bleeding time was numerically longer in the current protocol, where heparin was used along with tirofiban. The addition of heparin it tirofiban had the effect of substantially increasing the number of subjects with bleeding times >30 minutes, especially the higher dose of tirofiban. Both protocols measured bleeding times after 24 and 48 hours.

Table 6.1.3.12.2d.11 Comparison of %IPA and bleeding times from protocols #005 and #008[a].

Tirofiban regimen	Tirofiban 0.4/0.1		Tirofiban 0.6/0.15	
Infusion Time	24 hrs	48 hrs	24 hrs	48 hrs
Bleeding Time				
With Heparin (#008)	14.0	20.0	25.7	30.0
Without Heparin (#005)	9.8	13.0	19.8	15.4
BTE				
With Heparin (#008)	2.8	2.9	2.5	4.4
Without Heparin (#005)	2.2	2.6	3.9	3.3
% Subjects >30 mins				
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.

6.1.3.12.2d Primary Analyses of Protocol #008

Clinical Cardiac Events

There were no deaths during the trial. The table below shows the incidences of refractory ischemia and MIs during the study. Overall, no significant differences are evident between the groups. Almost half of the subjects in all groups had experienced recurrent angina prior to discharge in all groups.

Table 6.1.3.12.2d.12 Cardiac events in protocol[a] prior to discharge.

Clinical event	Tirofiban 0.4/0.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	All Tirofiban n=36	Pooled Heparin n=12
Hour 48				
Recurrent Angina	9 (43%)	8 (53%)	17 (47%)	6 (50%)
Refractory Ischemia	2 (10%)	1 (7%)	3 (8%)	0 (0%)
MI	1 (5%)	0 (0%)	1 (5%)	0 (0%)
Hospital Discharge				
Recurrent Angina	9 (43%)	9 (60%)	18 (50%)	9 (75%)
Refractory Ischemia	3 (14%)	1 (7%)	4 (11%)	0 (0%)
MI	3 (14%)	2 (13%)	5 (14%)	(00 %)

a. Data from NDA volume 1.47, ref. 7, table 22, and electronic datasets.

The number of cardiac procedures performed during the hospitalization is shown below for each group. A large proportion of all groups underwent angiography prior to discharge; the higher fraction being in the heparin-alone group. PTCA also occurred relatively frequently in all groups.

Table 6.1.3.12.2d.13 Cardiac procedures in protocol #008[a] prior to discharge

Clinical event	Tirofiban 0.410.1 +Heparin	Tirofiban 0.6/0.15 +Heparin	All Tirofiban	Pooled Heparin
Hour 48				
Recurrent Angina	9 (43%)	8 (53%)	17 (47%)	6 (50%)
Refractory Ischemia	2 (10%)	1 (7%)	3 (8%)	0 (0%)
MI	1 (5%)	(0%)	1 (5%)	0 (0%)
Hospital Discharge				
Recurrent Angina	9 (43%)	9 (60%)	18 (50%)	9 (75%)
Refractory Ischemia	3 (14%)	1 (7%)	4 (11%)	0 (0%)
MI	3 (14%)	(2 1 3 %)	5 (14%)	0 (0%)

a. Data from NDA volume 1.47, ref. 7, table 24, and electronic datasets.

6.1.3.13 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 number of subjects with any SAE was highest in the tirofiban 0.4/0.10 group. All of the discontinuations due to an AE, including lab AEs, were in the tirofiban groups. Drug-related AEs were higher in all three tirofiban groups than in the pooled heparin group. Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

Table 6.1.3.13.1 Clinical adverse experience (AE) summary from protocol #008[a].

Clinical event	Tirofiban (90.5) n=21	Tirofiban (1010.1) n=-15	Pooled Heparin n=12
With Any AE n(%)	14 (67)	9 (60)	9 (75)
With Serious AE	3 (14)	1 (7)	1 (8)
With Drug-Related AE[b]	3 (14)	2 (13)	1 (8)
With Serious and Drug-Related AEs	0 (0)	0 (0)	0 (0)
Discontinued due to an AE	1 (5)	2 (13)	0 (0)
Discontinued due to Lab AE	2 (1b	1 (7)	0 (0)

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. One subject, AN 242, experienced both clinical and lab AEs which led to D/C. Subject was included both here and in lab AEs.
d. Two subjects, AN 221 and 241, had clinical & lab AEs which led to discontinuation. Subject was included both here and in lab AEs.

6.1.3.13.2 Comments on Specific Safety Parameters

Deaths

There were no subject deaths.

Serious Adverse Events

There were 5 serious adverse events, none of which were bleeding-related. Narratives for these events are included below.

Tirofiban 0.4/0.1

1. AN 011 - Acute Myocardial Infarction (Day 1): A 61-year-old white male was hospitalized with unstable angina. Concomitant medication included heparin, aspirin, metoprolol, nitroglycerin IV, nitropaste, and isosorbide dinitrate. The patient developed refractory angina 18 hours after initiation of tirofiban infusion requiring premature termination of the study and urgent coronary angiography. Angiogram revealed 95% stenosis of proximal right coronary artery (RCA) with no thrombus noted. Additionally, the patient experienced a period of hypotension due to increased nitroglycerin. Heparin 5000 U IV bolus then 1000 to 1400 units/hour and IV nitroglycerin were initiated. Laboratory evaluation the next day revealed serum creatine kinase (CK) of 349 with CK-MB 18.6%. Percutaneous transluminal coronary angioplasty (PTCA) of right coronary artery (RCA) was complicated by occlusion of right ventricular (RV) branch and a subsequent RV infarct. Repeat angiography was complicated by ventricular tachycardia requiring cardioversion. The angiography showed RCA (main) open and RV branch closed. The patient's post-MI course was uncomplicated. He recovered and was discharged from the hospital. The investigator felt that the patient's experiences were life-threatening and not related to study drug therapy.

2. AN 016 - Acute Myocardial Infarction (Day 4): A 54-year-old Caucasian male was hospitalized with unstable angina. Concomitant medication included aspirin, heparin, metoprolol, lorazepam, morphine sulfate, nitroglycerin, and nitropaste. Approximately 18 hours after completion of study-drug infusion, the patient developed refractory angina requiring angiography. Post-angiography, the patient developed increased angina with ST-elevation. Serum CK (Peak CK=492) and electrocardiogram (ECG) results were suggestive of non-Q-wave myocardial infarction. The patient received seven separate doses of 1 to 4 mg of morphine sulfate and was found to be somnolent and hypotensive for 15 minutes prior to percutaneous transluminal coronary angioplasty (PTCA). The patient subsequently underwent PTCA of the right coronary artery. The post-PTCA course was uncomplicated. The investigator felt that the myocardial infarction was life-threatening and the patient's experiences were not related to study drug therapy.

3. AN 032 - Back Pain (Day 4): A 50-year-old female was hospitalized with unstable. Concomitant therapy included heparin, propranolol, aspirin, nitroglycerin, and lorazepam. She completed the 48-hour infusion without incident. Twenty-four hours post-infusion the patient completed an exercise treadmill study and reported that she had lower back pain and suprapubic pain. On examination the patient did not have any abdominal tenderness or rebound, but she reported noting a brief bloody discharge after urinating. Subsequent urine samples and laboratory analysis were negative. The patient was monitored for an additional 24 hours for back pain and suprapubic pain prolonging hospitalization. Subsequently she recovered and was discharged. The investigator felt that the patient's experience was not related to study-drug therapy.

Tirofiban 0.6/ 0.15

4. AN 107 - Acute Myocardial Infarction (Day 4): A 6 1 -year-old male was hospitalized with unstable angina. Concomitant medication included heparin IV Additional concomitant medication included amlodipine, nitropaste, aspirin, metoprolol, diltiazem, temazepam, and nitroglycerin. The patient responded well to study-drug therapy and antianginal therapy but suffered 'mild' hematuria following completion of study-drug infusion. Heparin was reinitiated following completion of the study and the patient underwent coronary angiography with PTCA to the distal RCA, mid-circumflex and first obtuse marginal arteries. The procedure was complicated by transient occlusion of the circumflex artery. Laboratory evaluation revealed CK 379 and CK-MB isoenzyme 12.0%. There were no other associated sequelae to prolong the patient's hospital stay. The investigator felt the myocardial infarction was life threatening and not related to study drug.

6.1.3.13.2 Comments on Specific Safety Parameters **(cont)**

Placebo

5. AN 038 - Readmission - Chest Pain (Day 5): A 42-year-old male smoker was hospitalized with unstable angina/non-Q-wave myocardial infarction. Concomitant therapy included lovastatin, aspirin, nizatidine, acetaminophen, nitroglycerin, heparin, diltiazem, lorazepam, oxycodone, acetaminophen, and morphine. The patient completed the 48-hour infusion without incident and.subsequently underwent cardiac catheterization. The patient had a 99% right coronary artery lesion with a thrombus. It was recommended that he remain on therapy with heparin for 48 hours, and undergo a PTCA. However, the patient left against medical advice. At home he experienced chest pain that did not subside with sublingual nitroglycerin. He presented to the emergency room and the chest pain was relieved with additional nitroglycerin. An electrocardiogram was normal. The patient was subsequently admitted to the hospital and underwent a successful PTCA. The patient recovered without complication. The investigator felt that the patient's rehospitalization was not related to study drug.

Bleeding Episodes

There were no bleeds that met the criteria for 'major bleeds' and no transfusions. During the tirofiban infusion, the incidence of bleeding was 4/36 (1 1%) in the tirofiban groups, compared with 1/12 (8%) in the heparin group. This should be compared with the incidence of bleeding in the protocol using tirofiban without heparin (protocol #005), which was 6% for both tirofiban alone and heparin alone.

Note that all of the subjects discontinued for bleeding adverse events were in the tirofiban groups.

Table 6.1.3.13.2 Clinical bleeding episodes in protocol 008[a].

'Treatment Group	Subject #	Site of Bleeding	Severity	Time of Onset	D/C'd?
MK (0.4/0.1) + Heparin (N=21)					
	010	Oral/Mouth Bleeding	Oozing	14.45 hrs	Y
	032	GU/Hematuria	Oozing	61.5 hrs	N
	040	Lip Laceration	Oozing	46 hrs	N
MK (0.6/0.15) + Heparin (N=15)					
	099	Laceration	Oozing	11 hrs	Y
		Ear	Mild	22.25 hrs	
		GU/Hematuria	Mild	26 hrs	
	106	Oral/Mouth	Mild	36 hrs	Y
		GI	Mild	39.5 hrs	
	107	GU/Hematuria	Mild	71 hrs	N
Placebo + Heparin (Pooled) **(N=12)**					
	087	Catheter Site	Mild	53 hrs	N
	093	Oral/Mouth	Mild	2 hrs	N

a. Data from NDA volume 1.47, ref 7, table 28 and electronic datasets.

Thrombocytopenia

There were no episodes of thrombocytopenia (<100,000 /mm^3) in the study.

6.1.3.14 Protocol 008 Efficacy Summary

This study was designed to assess the pharmacokinetics of tirofiban in subjects with UAPMQWMI, and to compare the effect of tirofiban on coagulation parameters with that of heparin. An important analysis in this protocol, using data from this protocol and protocol 005, was to determine if there was a significant interaction between tirofiban and heparin (pharmacokinetic, pharmacodynamic, or clinical).

pharmacokinetics

The clearance of tirofiban was similar in all three doses examined in the protocol. Similar to the results from protocol #005, older subjects had a significantly lower clearance of tirofiban (see table 6.1.3.12.2d.2). As in protocol #005, this difference may be due to decreased renal clearance of tirofiban in subjects >65 (the data are incomplete).

In the subjects in the two highest dose regimens of tirofiban , the bolus and infusion of tirofiban achieved high plasma concentrations of tirofiban within 30 minutes (see table 6.1.2.12.2d.1). No information about the plasma levels between 30 minutes and 24 hours are available. The plasma levels were stable at 24 and 48 hours in all tirofiban groups.

Pharmacodynamics

Both doses of tirofiban +heparin caused a >70% inhibition of platelet aggregation in almost all subjects, and had a significantly greater effect than did heparin. The lowest dose of tirofiban was less consistent effective in inhibiting platelet aggregation, (see table 6.1.3.12.2d.5). There is also a suggestion that the two highest dose groups had a greater effect to prolong bleeding time at the end of 2 hours (see table 6.1.3.12.2d.10), and that a higher fraction of the 0.6/0.15 tirofiban +heparin group achieved ≥70% IPA (see table 6.1.3.12.2d.7).

The calculated C_{50} for IPA was similar in this trial with protocol 005, suggesting that heparin administration does not affect the shape of the IPA-tirofiban dose curve.

Clinical endpoints

No inferences as to the efficacy of tirofiban can be drawn from the small numbers of clinical events. A large fraction of the population enrolled in the trial underwent cardiac procedures, including angiography and PTCA.

6.1.3.15 Protocol 008 Safety Summary

The small number of subjects makes overall assessment of safety difficult. There were no unexpected toxicities detected.

The most common bleeding AEs were minor. No large difference in the incidence of this AE was detected between the groups, although the tirofiban groups as a whole had a higher frequency of them than the heparin alone group (see table 6.1.3.13.2). The tirofiban groups did have a higher incidence of discontinuation for AEs, including lab AEs.

6.1.3.16 Protocol 008 Reviewer's Conclusions

1. Systemic clearance of tirofiban is independent of the doses used in this study. The impact of age on tirofiban clearance is not clearly established.

2. Tirofiban produces a >70% inhibition of ADP-induced platelet aggregation (IPA) in a high percentage of subjects at the two higher dosing regimens used (tirofiban 0.4/0.1 and 0.6/0.15). The higher dose is associated with a higher % of subjects with IPAs >30 minutes as well as a higher % of subjects with ≥70% IPA.

3. The use of tirofiban in this study was associated with a higher rate of discontinuation. These discontinuations included bleeding AEs.

6.2.1 Review of PRISM-PLUS Study

6.2.1.1 Title of Study

A multicenter, randomized, parallel, double-blind study to investigate the safety and clinical efficacy of MK-0383 in combination with heparin versus heparin alone with high-risk unstable anginainon-Q-wave myocardial infarction (PRISM-PLUS).

6.2.1.2 Sites of Investigation and Investigators

The list of investigators and sites is in NDA volume 1.37, Table A-l (pages A-6 to A-101). A list of subjects enrolled by site is in NDA volume 1.44, appendix 4.1 .1.

The PRISM-PLUS trial was performed at forty-seven centers internationally and 25 centers in the United States. An additional six centers (5 in the U.S., 1 non-U.S.) received study drugs but did not enroll any subjects. The table below summarizes the number of subjects enrolled according to the country.

T'able 6.2.1.2.1 Sit utilized during the PRISM-PLUS trial.

Country	Tirofiban n=345	Tirofiban + Heparin n=773	Heparin n=797
United States	58 (16.3%)	133 (17.2%)	**128** (16.1%)
Columbia	**7** (2.0%)	**11 (1.4%)**	**12** (1.5%)
Argentina	0 (0.0%)	**35 (4.5%)**	**38 (4.8%)**
Denmark	**4** (1.2%)	**9 (1.2%)**	9 (1.1%)
Finland	3 **(0.9%)**	11 (1.4%)	11 (1.4%)
Peru	**3 (0.9%)**	**23 (3.0%)**	**22 (2.8%)**
Spain	**31** (9.0%)	**38 (4.9%)**	**38 (4.8%)**
Mexico	**2 (0.6%)**	**14 (1.8%)**	**14 (1.8%)**
Canada	**211** (61.2%)	**403 (52.1%)**	**431 (54.1%)**
France	**10 (2.9%)**	19 **(2.5%)**	**19 (2.4%)**
Australia	**2 (0.6%)**	**2 (0.3%)**	**1** (0.1%)
South Africa	**7 (2.0%)**	**48 (6.2%)**	**45 (5.6%)**
Austria	1 (0.3%)	**2 (0.3%)**	**4 (0.5%)**
Switzerland	**6 (1.7%)**	**25 (3.2%)**	**25 (3.1%)**

6.2.1.3 Background

Initial protocol:

#006-02, submitted 8.17.94 internationally
#006-03, submitted 8.19.94 to the FDA

Amendment No. 1, submitted 12.20.94 internationally and 12.09.94 in the United States:
1. Changed the administration of study drugs peri-angiography and revascularization;
2. Added a 6-month follow-up;
3. Provided for the inclusion of non-Q-wave myocardial infarction (NQWMI) subjects, and
4. Changed the procedure for reporting Serious Adverse Events (SAEs).

Amendment No. 2, submitted 4.26.95 both internationally and in the United States:
1. Exchanged the primary and secondary endpoints so that the 7-day time point became the primary endpoint and the 48-hour time point became a secondary endpoint (along with the 30-day time point);
2. Expanded the defmition of refractory ischemia;
3. Added a prohibition of continuation of study drug during stent placement; and
4. Included a suggested duration of study drug administration to 108 hours.

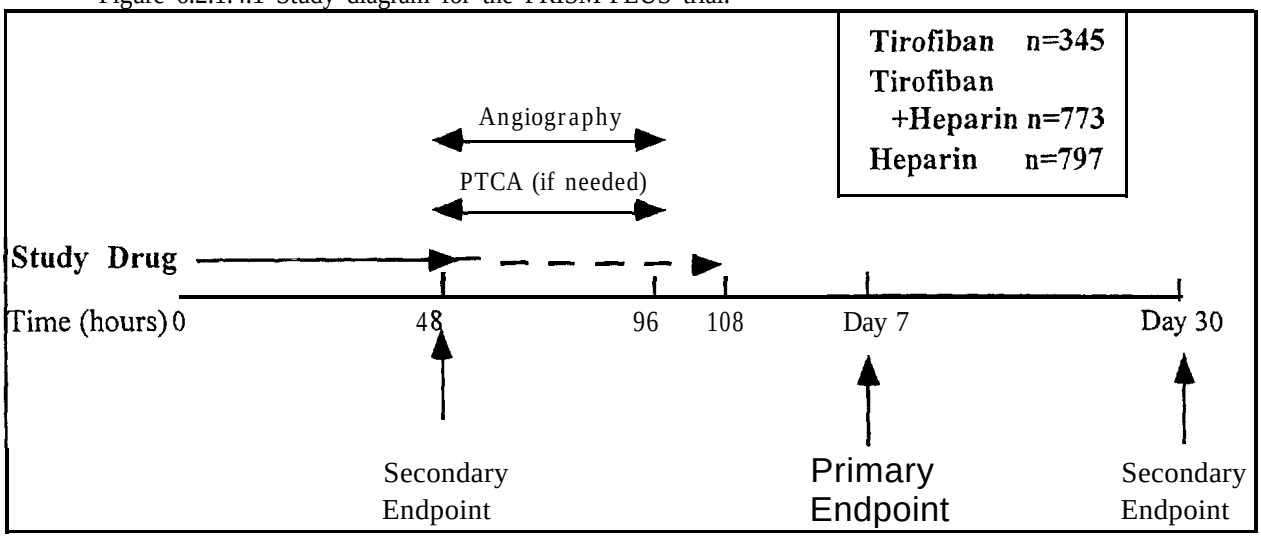
Interim analyses:

1. First interim analysis 6.28.95. Due to low pooled-group event rates, the efficacy results were not unblinded at this time (pooled group analyzed only).

2. Second interim analysis 11.13.95. At this time a decision was made to recommend termination of the tirofiban alone group and increase the size of the remaining two arms.

6.2.1.4 Study Design

Figure 6.2.1.4.1 Study diagram for the PRISM-PLUS trial.



General

The PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management in Subjects Limited by Unstable Signs and Symptoms) trial was a randomized, parallel, double-blind, multi-center, multi-national study that studied the efficacy of tirofiban in combination with heparin and aspirin for the management of subjects with unstable angina pectoris (UAP)/non-Q-wave myocardial infarction (NQWMI). In this study, 1915 subjects with unstable angina or NQWMI were randomized to receive tirofiban with heparin, tirofiban alone, or heparin alone. All subjects received aspirin, unless contraindicated for the individual subject. Randomized subjects were followed for 30 days after initiation of study drug for the occurrence of endpoints and adverse events. Subjects were then followed out to 180 days for the occurrence of clinical endpoints.

Subjects randomized to tirofiban alone received a loading dose of tirofiban of 0.6 μg/kg/min over 30 minutes followed by a maintenance infusion at 0.15 μg/kg/min. Subjects randomized to tirofiban and heparin received a loading dose of tirofiban of 0.4 μg/kg/min over 30 minutes followed by a maintenance infusion at 0.1 μg/kg/min and a 5000-U intravenous bolus of heparin followed by an initial maintenance infusion of 1000 U per hour. Subjects randomized to receive heparin alone received a 5000 U intravenous bolus of heparin followed by an initial maintenance infusion of 1000 U per hour. Heparin was adjusted by an unblinded coinvestigator to maintain the aPTT approximately 2X-control using a standard heparin nomogram. All aPTT results remained blinded to individuals directly responsible for subject care. Accordingly, the unblinded coinvestigator could not be involved with the subject's care (including reporting of clinical adverse experiences).

After 48 hours, all subjects, because of their high-risk clinical condition, *were* expected to undergo cardiac catheterization (unless contraindicated) with study drugs continuing throughout the procedure. In the event that a subject had a delay in the scheduling of routine diagnostic cardiac catheterization, they were to undergo the procedure no later than 96 hrs on study drugs (to allow for the minimal 12-hour infusion of the study drug post-intervention). In this situation, study drugs were administered for up to a total of 108 hours after initiation. Prior to angiography, subjects receiving tirofiban alone could receive a greater than or equal to 2500 U intravenous bolus of heparin to maintain the blind. (Subjects on heparin could receive a bolus of placebo.) Subjects not undergoing coronary angiography had the study drugs discontinued after 72 hours. After review of the angiographic data, subjects proceeded to immediate PTCA/atherectomy if indicated, or this procedure could have been delayed if clinical circumstances warranted. If stent placement was necessary for any reason, study drugs were discontinued as soon as the decision was made, since there had been no experience with the use or safety of tirofiban (with heparin and aspirin) when used concomitantly with dextran, warfarin, ticlopidine, or dipyridamole, drugs that might have been commonly used in the setting of stent placement.

If the subject required CABG or PTCA as a result of the angiography, the administration of heparin depended on the timing of the procedure. If the subject proceeded onto PTCA immediately, open-label heparin could be administered. If the procedure was to be delayed, the blinded heparin (or placebo) was stopped after the angiogram, and the femoral sheaths removed after at least 2 hours.

6.2.1.4 Study Design (cont)

General (cont)

Subjects were followed for the primary efficacy endpoint of the trial: the composite incidence of refractory ischemic conditions, new myocardial infarction, or death within 7 days of start of study drug. The secondary efficacy endpoints were the composite incidence of the same events at 48 hours and 30 days after start of study drugs (the 30-day secondary composite endpoint also included readmissions for unstable angina). The tertiary endpoint was the maximal extent of angiographically apparent thrombus. An exploratory analysis examined clinical outcomes of the subjects undergoing PTCA. As specified in the protocol, subjects were also followed up at 6 months after initiation of study drug for assessment of clinical status including death, rehospitalizations for myocardial ischemia/infarction, and any revascularization procedures.

Definitions of clinical events

Refractory Ischemic Conditions

A 'refractory ischemic condition' (RIC) during the hospitalization period was defined as any of the following clinical events:

a) Refractory Ischemia - defined as angina1 chest pain with ischemic ST-T changes (ST-segment depression or elevation of 20.1 mV or T-wave inversion or pseudonormalization >0. 1 mV above the isoelectric line in two contiguous leads on a 12-lead ECG) occurring as a single episode persisting for ≥20 minutes, or ≥2 episodes persisting for 210 minutes each within a l-hour period, despite optimal medical therapy. Optimal medical therapy was defined as that including, at least, an infusion of nitroglycerin plus a a-blocker or calcium channel blocker titrated to heart rate and blood pressure.

b) Hemodynamic Instability - defmed as clinical evidence of pulmonary edema, (new rales over one third lung fields), tachypnea (RR >30/min), evidence of hypoxemia (on oximetry or arterial blood gas), 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 electrocardiographic changes.

c) Severe, Prolonged or Repetitive Anginal Pain - defined as severe, prolonged or repetitive chest pain at rest (three or more episodes over a 24-hour period with at least one episode at least 5 minutes in duration and one episode accompanied by ischemia), leading to an urgent invasive intervention within 12 hours of symptom onset of the last qualifying episode. Urgent invasive interventions included diagnostic catheterization, and/or intra-aortic balloon pump counterpulsation, PTCA, atherectomy, stent or CABG (primary and repeat revascularizations). The presence of either ventricular or atria1 arrhythmias did not suffice to be classified as a 'refractory ischemia' unless associated with (i.e., clinically supportive ofj one of the conditions described above. All new arrhythmias (not present at baseline) were classified as adverse experiences, however.

d) Hospital Readmission - Hospital Readmission - subjects discharged from the hospital and readmitted within the 6 months of study drug initiation with unstable angina were classified as having reached a study endpoint.

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 I-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 23 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 defmed as a rise in creatine kinase to 250% above the preceding sample and which was at least ≥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.

6.2.1.4 Study Design (cont)
Definitions of clinical events (cont)

Ischemic Episodes

All subject-reported episodes of angina during hospitalization (i.e., chest pain suggestive of myocardial ischemia requiring administration, adjustments, or additions of antianginal medication) were recorded from the initiation of study drug through discharge. Any non-routine electrocardiograms were recorded on the case report form and any ischemic changes were reported.

Revascularization

Revascularization with coronary angioplasty, atherectomy, stent, or bypass surgery were recorded if occurring within 30 days or 6 months after initiation of study drug. The indication for these procedures was also recorded, in particular, whether or not the procedures were performed for recurrent pain or compelling anatomic indications (e.g., >90% stenosis in the proximal segment of either the left anterior descending, dominant left circumflex or right coronary artery).

Angiographic Endpoints

1) Maximal extent of angiographically apparent thrombus

Intracoronary thrombus was defined as an intraluminal filling defect visible during at least one complete cine run (a globular intraluminal radiolucency resulting in a recent occlusion or with a rounded on polypoid shape and protruding into the vessel lumen). Extent of apparent thrombi were classified as absent, possible, small, medium, large, recent total occlusion, or chronic total occlusion.

2) TIMI-Flow Grade

TIMI-flow grade was subclassified as either total occlusion, minimal perfusion, partial perfusion, or complete perfusion.

3) Reading of angiograms

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, rating the severity of the culprit lesion quantitatively by measuring percent diameter stenosis and minimal luminal diameter of the culprit lesion.

Clinical lab testing

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.

6.2.1.5 Primary and Secondary Endpoints

Primary endpoint

1. The incidence of refractory cardiac ischemia, new myocardial infarction, or death within 7 days of start of study drug.

Refractory cardiac ischemia included: 1) prolonged or repetitive angina1 chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy (including, at least, an infusion of nitroglycerin plus use of a B-blocker or calcium channel blocker titrated to heart rate and blood pressure); 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.

In the original protocol, dated 8.19.94, the primary endpoint was the incidence of refractory ischemic conditions, new myocardial infarction, or death within 48 hours of start of study drug. The 7 day outcome was listed as a secondary endpoint. The two endpoints were switched 4.26.95 as part of a protocol amendment.

Secondary endpoints

1. The incidence of refractory ischemic conditions, new myocardial infarction, or death at 48 hours after starting study drug.

2. The incidence of refractory ischemic conditions, new myocardial infarction, readmissions for unstable angina or death at 30 days after starting study drug.

Tertiary endpoints

1. The maximal extent of angiographically apparent thrombus.

6.2.1.5 Primary and Secondary Endpoints **(cont)**

Exploratory endpoint

1. Clinical outcomes of the subjects undergoing PTCA at the 6 month follow-up, including: death; rehospitalizations for myocardial ischemia/infarction; and any revascularization procedures.

6.2.1.6 Number of subjects/ randomization

Table 6.2 I .6. I Subjects enrolled in the PRISM-PLUS trial

Tirofiban	Tirofiban + Heparin	Heparin
n=345	n=773	n=797

Initially, randomization of 1260 subjects into three treatment groups was planned: tirofiban alone (n=420), heparin alone (n=420), or tirofiban and heparin (n=420). The true event rate in the heparin group of the PRISM-PLUS trial was assumed to be 35%. With 420 subjects per treatment arm, this trial has >90% power to detect a 30% reduction in the event rate in either the tirofiban-alone or the tirofiban +heparin groups at the 5% (2-sided) significance level. In addition, the trial has >80% power to simultaneously detect significant differences between tirofiban alone and tirofiban +heparin, and both groups when compared with heparin.

After 950 subjects were enrolled, the Data Safety Monitoring Board overseeing the trial recommended dropping the tirofiban alone arm, continuing the trial, and expanding the sample in the remaining arms (tirofiban + heparin and heparin alone), according to the protocol-specific rules (see Section 6.2.1.11.3 below). At that time, the heparin group had an event rate of 15.2%, which would require an increase in the sample size to 2205 in order to assure adequate study power. However, because of the termination of the tirofiban alone group, a total of 19 15 subjects with unstable angina or NQWMI were randomized to receive tirofiban with heparin (773 subjects), tirofiban alone (345 subjects), or heparin alone (797 subjects).

Subjects were randomly assigned via a computer-generated allocation schedule. Randomization was to occur within 12 hours after the last episode of chest pain. Using a double-dummy technique, study drug was prepared so that each subject received two infusion solutions administered simultaneously. The first solution (Bag 1) contained either tirofiban or placebo and the second solution (Bag 2) contained either heparin or placebo.

For all randomized subjects, the aPTT was measured at several times after initiating study drug(s). For subjects randomized to one of the groups receiving heparin, an unblinded coinvestigator adjusted the heparin infusion (Bag 2) to maintain the aPTT approximately 2X control using a standard nomogram (see protocol, reference 5, appendix 3.2.1 for details). Dummy instructions were provided to the unblinded coinvestigator for subjects randomized to tirofiban alone to adjust the 'placebo for heparin' infusion in Bag 2. All aPTT results remained blinded to individuals directly responsible for subject care. Accordingly, the unblinded coinvestigator could not be involved with the subject's care (including reporting of clinical adverse experiences).

At the time of the first interim analysis of the efficacy data, the Data Safety Monitoring Board (DSMB) overseeing the trial recommended dropping the tirofiban-alone arm due to an apparent excess mortality in this arm at 7 days. The sample size of the study was also increased to 735 subjects per remaining treatment group at this time.

6.2.1.7 Inclusion/ Exclusion Criteria

Inclusion criteria for PRISM-PLUS

1. Subjects who presented to the hospital with prolonged or repetitive chest pain and clearly documented ST-T wave changes or enzyme elevations indicating either unstable angina or NQWMI.

All subjects were required to have angina1 symptoms suggestive of cardiac ischemia within 12 hours prior to randomization, with one or more of the following presentations:

a) Accelerated pattern of angina1 pain (episodes of angina that were more frequent, severe, longer in duration, and/or precipitated by less exertion);

b) Prolonged (≥20 minutes) or recurrent angina1 pain at rest or with minimal effort; or

c) Angina1 pain at rest or with minimal exertion occurring >48 hours (but within 14 days) after an acute Q-wave myocardial infarction.

2. All unstable angina subjects were required to have ECG evidence of myocardial ischemia manifested by at least one of the following:

a) New or persistent or transient ST-segment depression ≥0.1 mV (0.08 seconds after the J-point) in at least two extremity leads or three precordial leads;

b) Transient or reversible (<20 minutes) ST-segment elevation ≥0.1 mV (0.08 seconds after the J-point) in at least two extremity leads or three precordial leads; or

c) New or persistent or transient T-wave inversion 20.3 mV (or pseudonormalization ≥0.1 mV above the isoelectric line) in at least three extremity leads or three precordial leads (excluding V1) or any combination of four anatomically consistent extremity and precordial leads (excluding Vl).

6.2.1.7 Inclusion/ Exclusion Criteria (cont)

Inclusion criteria for PRISM-PLUS (cont)

3. In addition, all unstable angina subjects were required to have at least one of the following 'high-risk clinical features:

a) Prolonged (≥20 minutes) anginal pain at rest or with minimal exertion with ischemic ECG changes;

b) Repetitive (within 12 hours) angina1 pain at rest or with minimal exertion of at least 5 minutes duration with a qualifying episode accompanied by ischemic ECG changes;

c) Angina1 pain at rest or with minima1 exertion with transient (<20 minutes) ST-segment elevation; or

d) Angina1 pain at rest or with minimal exertion with persistent (>20 minutes) ST-depression or evolving ST-T wave changes (>20 minutes) resulting in new persistent ischemic T-wave inversions (e.g., 'proximal LAD syndrome').

4. Subjects presenting with a history of UAPMQWMI meeting Inclusion Criteria 1, but not meeting any of Inclusion Criteria 2 or 3 were eligible to enter the trial if their CPK-MB fraction at the time of enrollment (within 12 hours of the last episode of chest pain) was elevated (>5% of total CPK, or greater than upper limit of normal for CPK-MB) or total CPK was ≥2 times the upper limit of normal. It was expected that a certain number of subjects who presented with angina1 pain and ST-segment deviation or T-wave inversion would have creatine kinase (CK) elevations consistent with a non-Q-wave myocardial infarction. Evidence of non-Q-wave infarction did not exclude the subject from the study.

5. Subjects must:

a) Have had their most recent episode of angina1 pain occur within 12 hours of randomization; and

b) Have been ≥ 18 years of age.

Exclusion criteria for PRISM-PLUS

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) 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 20.1 mV in two contiguous leads persisting for ≥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) Subjects with uncontrolled severe (resulting in hemodynamic instability) cardiac arrhythmias.

7) Heparin allergy or intolerance (including heparin-induced thrombocytopenia).

8) Thromholytic therapy within 48 hours prior to enrollment.

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 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).

6.2.1.7 Inclusion/ Exclusion Criteria (cont)

Exclusion criteria for PRISM-PLUS (cont)

11) 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). Subjects with cardiogenic shock were also excluded.

12) Subjects with hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease.

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

14) Subjects 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^3;

d) Prothrombin time >1.3 X control (INR>1.5).

15) Subjects receiving another investigational drug within 4 weeks prior to the study (including any prior 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 interfere with optimal participation in the study or produce a significant risk to the subject.

17) Inability to give informed consent.

6.2.1.8 Dosage/ Administration

The three phase III trials submitted in the NDA utilized three separate dosing regimens for tirofiban, as seen in the table below. See appendix 10, page 370, for discussion of the regimen of tirofiban and heparin used in each of the Phase III studies.

Table 6.2.1.8.1 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 Unit (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)[a] 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.

The study drugs 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

Subjects randomized to tirofiban alone received a loading dose of tirofiban at 0.6 µg/kg/min over 30 minutes. After 30 minutes, the infusion rate was adjusted downward to 0.15 µg/kg/min.

Tirofiban plus heparin

Subjects randomized to tirofiban and heparin received a loading dose of tirofiban of 0.4 µg/kg/min over 30 minutes followed by a maintenance infusion at 0.1 µg/kg/min and a 5000 U intravenous bolus of heparin followed by an initial maintenance infusion of 1000 U per hour.

6.2.1.8 Dosage/ Administration (cont)

Heparin alone

Subjects randomized to receive heparin alone received a 5000 U intravenous bolus of heparin followed by an initial maintenance infusion of 1000 U per hour. Heparin was adjusted by an unblinded coinvestigator to maintain the aPTT approximately 2X-control using a standard heparin nomogram. All aPTT results remained blinded to individuals directly responsible for subject care. Accordingly, the unblinded coinvestigator could not be involved with the subject's care (including reporting of clinical adverse experiences).

Aspirin (ASA) administration

All subjects, regardless of prior ASA use, received 300 to 325 mg of ASA approximately 30 minutes before initiation of study drug (unless the subject had received ASA in the hospital within 24 hours of initiation of study drugs), and after 24 and 48 hours of the study drug infusion, unless contraindicated. ASA was continued daily, thereafter, for at least 6 months at a dose of 80 to 325 mg, unless contraindicated.

6.2.1.9 Duration/ Adjustment of Therapy

In the PRISM-PLUS trial, study drug was to commence within 12 hours of the last episode of chest pain and could be continued for up to 108 hours. Subjects were to receive a minimum of 48 hours of therapy, during which time they were not to undergo cardiac catheterization unless they developed refractory ischemia or a new myocardial infarction. After 48 hours, all subjects were expected to undergo cardiac catheterization. Subjects who did not undergo angiography had study drug discontinued after 72 hours. Subjects undergoing PTCA had study drug continued for 12 to 24 hours following completion of PTCA. Subjects undergoing CABG or and those that were managed medically were to have study drug discontinued after angiography. As discussed above, heparin therapy was adjusted to maintain aPTT 2X control using a standard nomogram provided to the investigators.

Discontinuation of therapy

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

1) A condition that necessitated thrombolytic therapy, including acute closure during PTCA.

2) A decision to proceed to emergent coronary artery bypass surgery or to manage the subject's cardiac ischemia medically.

3) Need for intra-aortic balloon counterpulsation or percutaneous bypass.

4) PTCA/atherectomy after 84 hours of drug therapy (i.e., inability to meet the minimal 12-hour window for infusion of the tirofiban/placebo postintervention.

5) Any coronary stent placement.

6) 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.

7) Clinically relevant bleeding (or a significant decrease ≥4 grams/dl in hemoglobin levels from predrug values).

8) Significant thrombocytopenia (repeated/confirmed platelet count $<90{,}000/mm^3$).

In the event the subject was discontinued prematurely, all examinations which were to have taken place after 96 hours were performed (physical examination, 12-lead ECG, complete laboratory evaluation including PT and aPTT). Additionally, one plasma sample was collected immediately prior to cessation of study drugs and another 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.

6.2.1.10 Safety and Efficacy Endpoints Measured

Table 6.2.1.10.1 Timetable or clinical observatic s and ab me urem its in e PRI M-PI 'Strial".

Time after infusion (hrs)	Pre-infusion	0	6	12	2 4	4 8	72	8 4	96	120	Day 7	Day 30	Month 6
Test Performed													
Infusion of study drug(s)		X					(X)[c]	(X)[c]	(X)[c]				
ASA (80 to 325 mg/day)	X				X	X	X	X	X	X			
Angiography						(X)[d]	(X)[d]	(X)[d]					
History	X												
Physical exam	X				X	X	X		X				
ECG	X				X	X	X		X				
PT/aPTT	X		X	X	X	X	X		X				
CPK with isoenzymes	X				X	X							
Labs & hematology[e]	X		X		X	X	X		X	X			
Plasma tirofiban [b]													
Adverse event (AE) reporting		x	x	x	X	X	X	X	X				
Endpoint/ serious AE reporting		x	x	X	X	X	X	X	X	X	X	X	X

a. Data from NDA vo ne 1.42, page 2533.

b. Plasma tirofiban le s also drawn at time of premature discontinuation.

c. The timing of the end of study drug infusion depended on the treatment of each subject after angiography.

d. Angiography was to take place 48 hours after starting the infusion. If this was not possible for administrative reasons, up to 96 hours was allowed.

e. 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.

Note that AEs were not collected at the 6 month follow-up. The last 6 month follow-up was completed on May 20, 1997. The case report cutoff for the 6-month data was September 2, 1997.

6.2.1.11 Statistical Considerations

Analytical Methods

For the clinical endpoint analyses, the statistical significance of the differences between treatment groups was assessed using a logistic regression analysis. The dependent variable was an indicator of whether or not the subject experienced the specific endpoint. The independent variables included an indicator of treatment group and the following two covariates:

a) Antecedent use of heparin (No = 0, Yes = 1) prior to randomization;

b) Antecedent use of aspirin (No = 0, Yes = 1) prior to hospital admission.

Since the study was not designed to detect statistically significant results within subgroups, p-values within subgroups were not calculated. However, the differing effect of tirofiban plus heparin among subgroups (treatment-by-factor interactions) was analyzed using logistic regression, and tested at the 10% significance level. The sponsor hypothesized that the effect of tirofiban plus heparin on reducing the incidence of each of the three components of the composite endpoint would be similar. However, since two of the components (myocardial infarction and death) were expected to occur relatively infrequently, estimates of the drug effect for those two endpoints were expected to have large standard errors, potentially making it appear as though the drug effect differs greatly among components. For this reason it is important to statistically test for homogeneity of the effect in order to determine if the observed heterogeneity is greater than would be expected by chance alone.

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 independent variables in this model *were* the same as those used in the logistic regression, and, with the relatively low event rates observed in this study, the two models give very similar results. One important difference between the two models, however, is that while the drug effect is measured by the odds ratio when using logistic regression, it is measured by the hazard or risk ratio when using Cox regression.

Analytical Methods (cont)

The p-values for between-group comparisons for other variables were based on the following methods. For dichotomous variables (e.g., adverse experiences, cardiac procedures), Fisher's exact chi-square test was used. For categorical variables (e.g., race), chi-square test was used. For ordinal variables (e.g., most severe bleeding episode) and continuous variables (e.g., number of angina1 attacks, changes in vital signs), Wilcoxon rank-sum test was used. The mean number of angina1 attacks were compared between treatment groups with the Wilcoxon rank-sum test, and the proportions of subjects with cardiac procedures were compared using Fisher's exact test. In this review, all statistical results are per the sponsor's analysis, unless otherwise specified.

The primary analysis was an Intent to Treat (ITT) analysis for the primary endpoint. In addition, a selection of efficacy analyses were performed using a 'per-protocol population', which excluded a total of 73 subjects for the following reasons:

1. Did not meet inclusion criteria, including those who met inclusion criteria of ECG evidence of myocardial infarction (without enzyme elevation), but had no high-risk clinical features.
2. Did not take the study drug or discontinued study drug within 24 hours, without first experiencing a clinical endpoint.
3. Incorrect initial diagnosis (i.e., pulmonary embolism or pericarditis).

Plan for interim analysis and multiple comparisons

Two formal interim analyses were planned to be performed after 1/3 (420) and 2/3 (840) of the planned subjects had completed the trial. According to the usual O'Brien-Fleming boundary, the critical p-value required to reject the null hypothesis is 0.00059 at the first interim analysis, and 0.015 at the second interim analysis, and 0.047 at the final analysis.

Application of this stopping boundary is complicated by the fact that this trial has three treatment groups and two primary comparisons. As described in the 'Interim Monitoring Guidelines MK-383 Protocol 006,' (NDA vol. 1.74, pages 1347-1351), the p-values were to be modified so the p-value for both primary comparisons must be below the usual critical p-values at either interim analysis to declare statistical significance. There was no specific guideline for multiplicity adjustments at the interim analyses, but the protocol did specify the use of Holm's procedure to adjust for multiplicity in the (final) analysis of the primary endpoint. By Holm's procedure, the largest p-value will then be compared to alpha for assessing its significance. Presumably, the same procedure could be applied to each interim analysis.

There was no specific guideline as to the early termination of an individual arm, as this was thought to be unlikely at the planning stage of the PRISM-PLUS trial. According to the NDA report, the DSMB was requesting not to stop either of the tirofiban groups alone for overwhelming efficacy, but rather only to stop the trial if the results for both tirofiban groups reached statistical significance. As the sponsor argued and we agree, this guideline will undoubtedly make the repeated sequential testing of the null hypothesis conservative in the alpha level.

There was a protocol-specified rule for sample size re-estimation. Following the first interim analysis the DSMB would examine the event rate for the primary endpoint in the heparin group and make a recommendation according to the table below.

Table 6.2.1.11 Guidelines for re-estimation of PRISM-PLUS trial size, based on int rim event rates.

Heparin group event rate	Recommendation
230%	No change
225 to <30%	Increase total sample size to 1470
220% to <25%	Increase total sample size to 1764
515% to <20%	Increase total sample size to 2205
210% to 45%	Increase total sample size to 2940
25% to 40%	Increase total sample size to 4410
<5%	Increase total sample size to 8820

Interim decision to discontinue the tirofiban alone arm

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 on 6.28.95, 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.

6.2.1.11 Statistical Considerations

Interim decision to discontinue the tirofiban alone arm (cont)

This second interim analysis (the first look at the efficacy data) took place after 30-day efficacy results were available for just over 200 subjects per group on 11.13.95. At the time of this analysis, the DSMB recommended that the trial discontinue enrollment in one of the tirotiban treatment arms (it turned out to be the tirofiban-alone arm) due to an excess mortality at the 7-day endpoint. Using a protocol-specified rule (summarized above), the DSMB also recommended an increase in the sample size of the trial to 735 subjects per group. This recommendation to stop the tirofiban-alone was based on an observed a 7-day mortality rate in the tirofiban-alone group that was greater than in either of the other two treatment groups: 10 deaths among 210 subjects (4.8%) in the tirofiban group compared to 3 deaths among 213 subjects (1.4%) in the tirofiban plus heparin group and 3 deaths among 211 subjects (1.4%) in the heparin group. The comparison of tirofiban and heparin nearly achieved nominal statistical significance (i.e., without adjustment for multiplicity, p=0.056). The DSMB then requested updated, current mortality data on all randomized subjects. When these results showed a similar trend, the DSMB recommended that the tirofiban arm be discontinued. After extensive discussions, the recommendation was accepted by the Steering Committee. At the Steering Committee's request, the investigators and the sponsor's clinical research personnel involved in the trial remained blinded to the identity of the dropped arm (although it was known that the heparin arm was not the dropped arm). The last subject was randomized to the tirofiban arm on 12.08.95. The results on which this decision was based am discussed further in section 6.2.1.12.3 below (Subgroup & Post-hoc Analyses of the PRISM-PLUS Trial Results).

6.2.1.12 Efficacy Outcomes

6.2.1.12.1 Subject Demographics & Baseline Characteristics

The demographics and baseline characteristics of the subjects in the PRISM-PLUS trial are summarized in the following tables. Overall, the three groups were well-balanced as regards demographics and clinical presentation at the time of entry into the trial.

Table 6.2.1.12.1.1 Demographics of the PRISM-PLUS trial".

Demographic	Tirofiban (n=345)	Tirofiban + Heparin (n=773)	Heparin (n=797)	Combined (n=1915)
Gender				
Female	114 (33%)	254 (32.9%)	252 (31.6%)	620 (32.4%)
Male	231 (67%)	519 (67.1%)	656 (68.4%)	1295 (67.6%)
Race				
White	3 12 (90.4%)	664 (85.9%)	675 (84.7%)	1651 (86%)
Black	12 (3.5%)	32 (4.1%)	29 (3.6%)	73 (3.8%)
Asian	1 (0.3%)	3 (0.4%)	10 (1.2%)	14 (0.7%)
Hispanic	14 (4.1%)	38 (4.9%)	45 (5.6%)	97 (5.1%)
Other	6 (1.7%)	36 (4.7%)	38 (4.8%)	80 (4.2%)
common Diagnosis				
Hypertension	174 (50.4%)	427 (55.2%)	446 (56.0%)	1047 (54.7%)
Hypercholesterolemia	167 (48.4%)	385 (49.8%)	396 (49.7%)	948 (49.5%)
Family Hx of heart disease	193 (55.9%)	368 (47.6%)	348 (43.7%)	909 (47.5%)
Hx of MI	157 (45.5%)	345 (44.6%)	308 (38.6%)	810 (42.3%)
Diabetes	85 (24.6%)	169 (21.9%)	193 (24.2%)	447 (23.3%)
Anxiety	83 (24.1%)	184 (23.8%)	183 (23.0%)	450 (23.4%)
Tobacco Use	249 (72.2%)	554 (71.8%)	553 (69.6%)	1356 (71.0)

)ata from NDA volume 1.42, ref. 5, table 8, confirmed by FDA analysis.

Table 6.2.1.12.1.2 Baseline physical exam and vital signs in the PRISM-PLUS trial".

Demographic	Tirofiban (n=345)	Tirotiban + Heparin (n=773)	Heparin (n=797)
Age (mean±sd)	63.2±11.3	63.0±11.8	63.3±11.6
Height (cm)			
Males	171.8±7.0	172.0±7.3	171.4±8.3
Females	157.5±8.2	158.5±6.4	157.9±7.2
Weight (kg)			
Males	79.7113.2	80.0k13.8	80.9±14.8
Females	67.4±13.6	69.2±14.3	68.8±14.1
Supine BP			
Systolic	130.4±21.1	130.8±21.0	130.3±21.0
Diastolic	75.8±12.6	75.0±12.1	75.3±12.8
Pulse rate	72.9±14.4	72.4±13.4	72.3±13.9

a. Data from NDA volume 1.42, Tables 8 and 9, confirmed by FDA analysis.

Table 6.2.1.12.1.3 Inclusion criteria and duration of angina at time of entry into PRISM-PLUS".

Demographic	Tirofiban n=345	Tirofiban + Heparin n=773	Heparin n=797	Total n=1915
Inclusion Criteria				
Possible NQWMI	117 (33.9%)	239 (30.9%)	271 (34.0%)	627 (32.7%)
Evolving NQWMI[b]	40 (11.6%)	106 (13.7%)	98 (12.3%)	244 (12.7%)
UAP	188 (54.5%)	428 (55.4%)	428 (53.7%)	1044 (54.5)
ECG evidence of ischemia				
ST Segment depression	196 (57.1%)	440 (57.1%)	479 (60.3%)	1115 (58.4%)
ST Segment elevation	52 (15.2%)	113 (14.7%)	105 (13.2%)	270 (14.2%)
T-Wave inversion	199 (58%)	401 (52.1%)	416 (52.3%)	1016 (53.2%)
Elapsed Time: pain to study start				
<3 hrs	38 (11.0%)	113 (14.6%)	119 (15.0%)	270 (14.1%)
3 to 6 hrs	102 (29.6%)	236 (30.6%)	210 (26.4%)	548 (28.7%)
6to 12 hrs	179 (52.0%)	357 (46.2%)	412 (51.8%)	948 (49.6%)
12 to 18 hrs	22 (6.4%)	63 (8.2%)	51 (6.4%)	136 (7.1%)
18 to 24 hrs	1 (0.3%)	2 (0.3%)	1 (0.1%)	4 (0.2%)
>24 hrs	2 (0.6%)	1 (0.1%)	3 (0.4%)	6 (0.3%)

a. Data from NDA volume I.42, tables 8. Shown as n (%).

b. Evolving NQWMI was defined as presence of a high-risk anginal presentation without *enzyme* elevation at randomization, and enzyme evidence of an MI within 24 hours of study start without an intercurrent event classified as an endpoint by the Endpoint Committee.

6.2.1.12.2 Disposition and Follow-up for Subjects in PRISM-PLUS

Disposition

The first table below summarizes the disposition of the subjects in the PRISM-PLUS trial, including the reasons for discontinuation. Overall, there was no significant difference in the percentage of subjects discontinued prematurely between the tirofiban +heparin and heparin-alone arms. The rate of discontinuation due to a presumed clinical endpoint was higher in both the tirofiban-alone and the heparin-alone groups, compared with the tirofiban +heparin group (5.4% for heparin-alone vs. 2.5% for tirofiban +heparin, p=0.003). The rate of discontinuations for bleeding AE was significantly higher in the tirofiban +heparin group than in the heparin-alone group (3.5% vs. 1.3%, p=0.004). Details of the subject discontinuations can be found in the appendix 4, section 16.0.

6.2.1.12.2 Disposition and Follow-up for Subjects in PRISM-PLUS (cont)

Table 6.2.1.12.2.1 Disposition of subjects randomized in the PRISM-PLUS trial'.

Subject Disposition	Tirofiban' n=345	Tirofiban + Heparin n=773	Heparin n=797	Total n=1915
Randomized	345	773	797	1915
Completed	3.05 (88.4%)	658 (85.1%)	692 (86.8%)	1655
Discontinued (Total),	40 (11.6%)	115 (14.9%)	105 (13.2%)	260
Presumed clinical endpoint	16 (4.6%)	19 (2.5%)	43 (5.4%)	78
Non-bleeding clinical AE[b]	4 (1.2%)	19[d] (2.5%)	13 (1.6%)	36
Non-bleeding laboratory AE[b]	1 (0.3%)	3[e] (0.4%)	2 (0.3%)	6
Clinical or lab bleeding AE[c]	6 (1.7%)	27 (3.5%)	10 (1.3%)	43
Subject noncompliance	2 (0.6%)	4 (0.5%)	2 (0.3%)	8
Protocol deviation	4 (1.2%)	15 (1.9%)	15 (1.9%)	34
Subject withdrawn	1 (0.3%)	6 (0.8%)	7 (0.9%)	14
Did not receive drug	3 (0.9%)	7 (0.9%)	8 (1.0%)	18
Other reasons	3 (0.9%)	15 (1.9%)	5 (0.6%)	23

a. Based on a recommendation by the DSMB overseeing the trial, this arm was dropped after 345 subjects were entered.

b. Includes counts of subjects who discontinued due to nonbleeding clinical or nonbleeding laboratory adverse events, in their respective categories.

c. Includes clinical or laboratory adverse experiences.

d. One subject in this group discontinued due to atrial fibrillation (an ECG adverse event), but is counted as a clinical AE discontinuation.

e. One subject in this group discontinued due to asystole (an ECG AE), but is counted as a laboratory AE discontinuation.

f. Data from NDA volume 1.42, page 2501 and from electronic datasets.

Subject follow-up in the PRISM-PLUS 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 6.2.1.12.2.2 Summary statistics on duration of follow-up in PRISM-PLUS tri l".

	Tirofiban alone n=316	Heparin n=745	Tirofiban +Heparin n=731
<30 days	3.1%	4.1%	2.8%
≥30 days	96.9%	95.9%	97.2%
mean±sd	42±25	44±29	44±29
range	7-185	I-188	o-197
99th percentile	147	17.5	160
95th' percentile	106	120	115
75th percentile	38	38	39
50th percentile	34	34	34
25th percentile	32	32	32
5th percentile	31	31	31
1st percentile	31	8	29

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

6.2.1.12.2a Subject Selection

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

6.2.1.12.2b Protocol Violations & Deviations

Seventy-three subjects are not included in the secondary, per protocol, analyses, for the reasons listed below.

Table 6.2.1.12.2b.1 Reasons for subject exclusion from the 'per protocol' analyses in PRISM-PLUS[a].

Reason for exclusion	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin[b] n=797
Excluded for any reason	12 (3.5%)	31 (4.0%)	30 (3.8%)
Excluded for failure to meet inclusion criteria	2 (0.6%)	7 (0.9%)	6 (0.8%)
Excluded for no study drug received	3 (0.9%)	7 (0.9%)	8 (1.0%)
Excluded for <24 hrs of study drug received	7 (2.0%)	17 (2.1%)	17 (2.1%)

a. Data from NDA 20-912, volume 1.42, ref. 5, tables 14 and volume 1.59, reference 55, table 1.

b. One heparin-alone subject received heparin for <24 hours

6.2.1.12.2c Concomitant Therapies used after Trial Initiation

The median length of hospital stay was 8 days in both groups. The mean length of stay, measured from the start of the study to the time of hospital discharge were similar among the three groups: tirofiban alone, 11.7±9.7; tirofiban +heparin, 10.6±8.9; and heparin alone 11.2±10.0.

The time from onset of angina1 pain until receipt of study drug was <12 hours in over 90% of all subjects, as seen from the table below.

Table 6.2.1.12.2c.1 Time to administration of study drug after onset of pain in the PRISM-PLUS study[a].

Elapsed time (hrs)	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	Total n=1915
<3 hrs	38 (11.0%)	113 (14.6%)	119 (15.0%)	270 (14.1%)
3 to 6 hrs	102 (29.6%)	236 (30.6%)	210 (26.4%)	548 (28.7%)
6 to 12 hrs	179 (52.0%)	357 (46.2%)	412 (51.8%)	948 (49.6%)
12 to 18 hrs	22 (6.4%)	63 (8.2%)	51 (6.4%)	136 (7.1%)
18 to 24 hrs	1 (0.3%)	2 (0.3%)	1 (0.1%)	4 (0.2%)
>24 hrs	2 (0.6%)	1 (0.1%)	3 (0.4%)	6 (0.3%)

a. Data from NDA volume 1.44, appendix 4.1.2.

The duration of study drug infusion was also similar among the three groups, as shown in the table below. This analysis was based on the per-protocol subject population, as detailed above (section 6.2.1.11).

Table 6.2.1.12.2c.2 Duration of study drug infusion in the PRISM-PLUS trial[a].

Duration of study drug administration (hrs)	Tirofiban	Tirofiban +Heparin	Heparin
All Subjects (mean±SD)	72.1±19.7 n=342	71.3±20.8 n=766	71.3±20.0 n=789
Subjects undergoing specific procedures			
Angiography (mean±SD)	73.7±18.8 n=312	72.3±20.3 n= 692	72.6±19.3 n=704
No Angiography (mean±SD)	57.2±22.8 n=30	61.8±23.4 n=74	60.5±22.0 n=85
Any Revascularization (mean±SD)	76.2±19.0 n=198	73.0±21.0 n=425	73.0±20.1 n=419
PTCA (mean±SD)	79.0±19.5 n=109	76.6±19.8 n=237	76.0±19.0 n=236
CABG (mean±SD)	72.2±19.0 n=82	69.5±21.5 n=179	68.9±20.6 n=181

a. Data from NDA 20-912, volume 1.42, ref. 5, tables 16.

The sponsor also summarized the amount of heparin administered to each group. No significant differences between the groups were detected.

Table 6.2.1.12.2c.3. Dose of heparin administered in the PRISM-PLUS trial.

Measurement	Tirofiban	Tirofiban +Heparin	Heparin
Number of heparin/placebo boluses	1.2±1.0	1.3±1.5	1.4±1.4
Number of heparin/placebo boluses prior to angio	0.7±0.6	0.7±0.5	0.7±0.5
Units of heparin (boluses)	NA	6155±7051	6439±6801
Units of heparin (infusion)	NA	70310±26729	70606±27740
Units of heparin (combined)	NA	76465±29654	77044±30600

a. Data from NDA 20-912, volume 1.42, ref. 5, appendix 4.1.6, and at request from sponsor to medical reviewer. NA-not available.

Next, the sponsor compared the activated partial thromboplastin times between the three groups at hours 6, 12, 24, 36, 48, 72, and 96 hours after start of study drug infusion. At all time points, the aPTT for the tirofiban alone was significantly less than for the two regimens using heparin (average25-30 at all time points). There was no significant difference in the average aPTT at any time point between tirofiban +heparin and heparin. At all time points ≤24 hours, the average aPTT for both groups was 65-70 secs. The highest average aPTT was after 6 hours (82±47 and 80±46 for the combination group and the heparin alone groups, respectively).There was also no significant difference in the % of subjects with markedly prolonged aPTT (>120 secs) between the combination and heparin alone groups (averaging approximately 5% of all subjects at ail time points≥24 hours in both groups, see NDA volume 1.42, ref 5, appendix 4.1.7).

6.2.1.12.2c Concomitant Therapies used after Trial Initiation **(cont)**

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 1.42, ref 5, table 12 for full listing). ß-blockers were used during the course of the trial by 78% of the total study population, calcium channel blockers by 47%, nitrates by 95%, and aspirin products by 98%. The most common individual concomitant therapies were aspirin (used by approximately 88% of the total study population), nitroglycerin (88%), heparin (approximately 61%), acetaminophen (52%) and metoprolol tartrate (48%).

The treatment groups were generally comparable with respect to concomitant therapies, although more tirofiban + heparin subjects than heparin subjects took concomitant calcium channel blockers (49% vs. 43%; p=0.020), anti-inflammatory agents (5.3% vs. 2.6%; p=0.009), and the angiotensin converting enzyme inhibitors captopril (9.6% vs. 6.3%; p=0.019) and lisinopril (3.9% vs. 2.1%; p=0.053). Additionally, more subjects in the combination group received vancomycin hydrochloride (1.4% vs. 0.4%; p=0.032), and glipizide (1.2% vs. 0.3%; p=0.035).

6.2.1.12.2d Primary Analyses of the PRISM-PLUS Trial Results

In the PRISM-PLUS trial the pre-specified, the primary endpoint was the incidence of refractory cardiac ischemic conditions (RIC), recurrent myocardiai infarction (MI), or death from any cause within 7 days of the start of study drug. The proportions of subjects who met the composite endpoint by 7 days was 100/773 (12.9%) in the tirofiban +heparin group and 143/797 (17.9%) in the heparin-alone group. This difference between treatments has an odds ratio of 0.660, which represents a 33% risk reduction for an event for the tirofiban group (p=0.004). The table below summarizes the incidence of this endpoint at 48, 7, 30, and 180 days. The p values for these comparisons have been confirmed by FDA analysis.

Table 6.2.1.12.2d.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".

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	Odds ratio & 95% CI[e]	p value (T+H vs H)[b]
Composite endpoint at 48 hours[d] (specified secondary endpoint)	26 (7.5%)	44 (5.7%)	62 (7.8%)	0.692 0.462, 1.034	0.073
Composite endpoint at 7 days (specified primary endpoint)	59 (17.1%)	100 (12.9%)	143 (17.9%)	0.660 0.499, 0.874	0.004
Composite endpoint at 30 days (specified secondary endpoint)	81 (23.5%)	143 (18.5%)	178 (22.3%)	0.769 0.599, 0.987	0.039
Composite endpoint at 180 days	105 (30.4%)	214 (27.7%)	256 (32.1%)	0.811 0.677, 0.973	0.024
RIC at 48 hours	23 (6.7%)	37 (4.8%)	47 (5.9%)	0.774 0.496, 1.209	0.26
RIC at 7 days	39 (11.3%)	72 (9.3%)	101 (12.7%)	0.685 0.495, 0.946	0.022
RIC at 30 days'	44 (12.8%)	82 (10.6%)	107 (13.4%)	0.741 0.543, 1.010	0.058
RIC at 180 days'	44 (12.8%)	82 (10.6%)	107 (13.4%)	0.755 0.566, 1.007	0.056
MI (both fatal and non-fatal) at 48 hours	5 (1.4%)	6 (0.8%)	19 (2.4%)	0.313 0.124, 0.790	0.014
MI (both fatal and non-fatal) at 7 days	24 (7.0%)	30 (3.9%)	56 (7.0%)	0.528 0.335, 0.833	0.006
MI (both fatal and non-fatal) at 30 days	31 (9.0%)	51 (6.6%)	73 (9.2%)	0.696 0.479, 1.010	0.057
MI (both fatal and non-fatal) at 180 days	35 (10.1%)	64 (8.3%)	84 (10.5%)	0.761 0.549, 1.053	0.100
Death at 48 hours	2 (0.6%)	1 (0.1%)	2 (0.2%)	0.509 0.046, 5.634	0.58
Death at 7 days	16 (4.6%)	15 (1.9%)	15 (1.9%)	1.010 0.489, 2.086	0.98
Death at 30 days	21 (6.1%)	28 (3.6%)	36 (4.5%)	0.784 0.473, 1.301	0.35
Death at 180 days	25 (7.2%)	53 (6.9%)	56 (7.0%)	0.965 0.663, 1.406	0.85

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

b. p value per sponsor using logistic regression analysis, and confirmed by FDA 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.

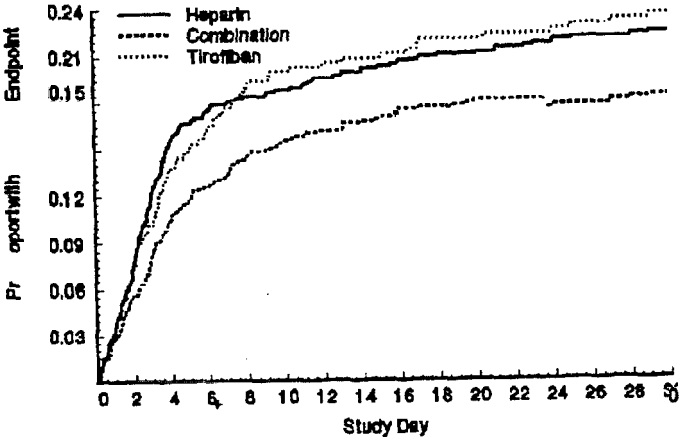
f. The incidence of RIC was the same at 30 and 180 days, because the subjects experiencing recurrent anginal events were classified as recurrent UAP, not RIC, after hospital discharge (per protocol).

6.2.1.12.2d Primary Analyses of the PRISM-PLUS Trial Results

The sponsor also performed an analysis of the time course of the effect of tirofiban and heparin on the primary endpoint and its components. The next two figure show the time course of the occurrence of the primary endpoint out to 30 days, and then out to 180 days.

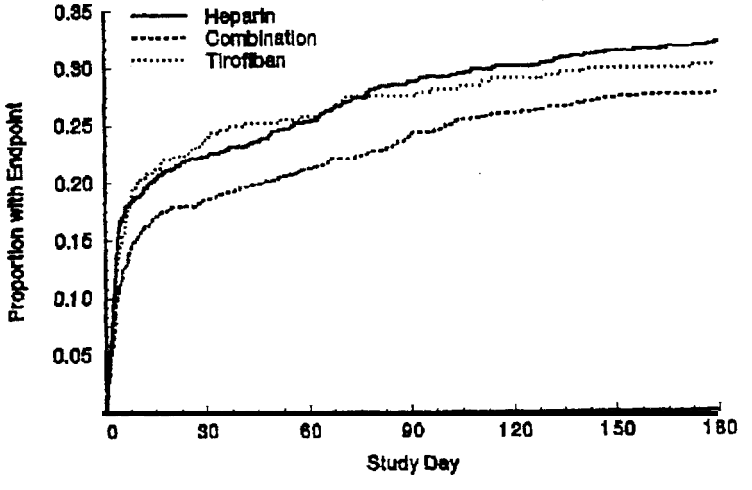
The first figure shows the incidence of the composite endpoint from day 0 through day 30.

Figure 6.2.1.12.2d.1 Incidence of the composite endpoint (RIC/MI/Death) for days O-30 in the PRISM-PLUS trial.



The next figure shows the incidence of the composite endpoint out to 180 days.

Figure 6.2.1.12.2d.2 Incidence of the composite endpoint (RIC/MI/Death) for days O-180 in the PRISM-PLUS trial.



6.2.1.12.3 Subgroup & Post-hoc Analyses of the PRISM-PLUS Trial Results

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.

Table 6.2.1.12.3.1 Incidence of the primary endpoint (RIC/MI/Death) and MI/ Death at 48 hours, 7, 30, and 30 days in the PRISM-PLUS trial analyzed for significance using Pearson's chi square[a,c,d].

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	p value by chi square (T+H vs H)[b]
Composite endpoint at 48 hours[d] (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 reference 55, tabl 1. Intent-to-treat population is used.

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

c. RIC: refractory ischemic conditions included: (I) 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.

The sponsor also performed a series of supportive analyses, which are shown below.

Per-protocol analysis of composite endpoint

The primary endpoint and it's components were analyzed on a per-protocol population, as detailed in the statistical section above (section 6.2.1.11). This analysis excludes subjects who did not receive study drug at all, or received it for <24 hours before discontinuation (without meeting a clinical endpoint). The results are consistent with the primary ITT analysis.

Table 6.2.1.12.3.2 Incidence of the primary endpoint (RIC/MI/Death) and its components at 7 days in the PRISM-PLUS trial, based on a per-protocol population analysis[a].

Endpoint	Tirofiban n=333	Tirofiban +Heparin n=742	Heparin n=767	p value (T+H vs H)[b]
Composite endpoint	57 (17.1%)	100 (13.5%)	139 (18.1%)	0.006
Composite/ procedures endpoint	56 (16.8%)	95 (12.8%)	131 (17.1%)	0.010
Composite/ revascularization endpoint	45 (13.5%)	69 (9.3%).	99 (12.9%)	0.016
Refractory Ischemic Conditions	39 (11.7%)	72 (9.7%)	98 (12.8%)	0.032
MI (both fatal and non-fatal)	23 (6.9%)	30 (4.0%)	56 (7.3%)	0.006
MI (fatal only)'	4 (1.2%)	8 (1.1%)	7 (0.9%)	0.80
Death	15 (4.5%)	15 (2.0%)	13 (1.7%)	0.

a. Data from NDA 20-912, volume 1.42, reference 5. aqoendix 4.1.10.

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

c. Fatal MI refers to MI associated with death within 7 days.

Further analyses of clinical benefit

Two analyses, the incidence of readmission for UAP and the incidence of MI/Death, are useful to compare the effects of tirofiban with those of other compounds in this class. There was no significant effect of tirofiban on the incidence of readmission for UAP, especially through the 180 day time point. Tirofiban had a nominally significant effect on the incidence of MI/ Death at days 2,7 and 30.

Table 6.2.1.12.3.3 Incidence of the readmission for UAP and MI/Death in the PRISM-PLUS trial[a].

Endpoint	Tirofiban n=345	Tirofiban +Heparin n=773	Heparin n=797	Odds ratio & 95% CI[c]	p value (T+H vs H)[b]
Readmission for UAP at 30 days	9 (2.6%)	16 (2.1%)	11 (1.4%)	1.463 0.673, 3.180	0.34
Readmission for UAP at 180 days	33 (9.6%)	84 (10.9%)	85 (10.7%)	1.004 0.742, 1.357	0.98
MI/Death at 48 hours	6 (1.7%)	7 (0.9%)	21 (2.6%)	0.330 0.139, 0.783	0.012
MI/Death at 7 days	36 (10.4%)	38 (4.9%)	66 (8.3%)	0.565 0.374, 0.854	0.007
MI/Death at 30 days	47 (13.6%)	67 (8.7%)	95 (11.9%)	0.695 0.499, 0.967	0.031
MI/Death at 180 days	55 (15.9%)	95 (12.3%)	122 (15.3%)	0.775 0.593, 1.014	0.063

a. Data from NDA 20-912, volume 1.42, tables 17 and volume 1.59, reference 55, table 1.1 en&to-treat popul[illegible]on is used.
b. p value per sponsor using logistic regression analysis, comparing heparin vs the combination group, confirmed by FDA analysis.
c. Odds ratio shown in bold for tirofiban +heparin vs. heparin.

Withdrawal of the 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, is summarized in the table below, reflecting the subjects entered into the trial by September 30, 1995. 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 apparent increased 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 fi-action 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 6.2.1.12.3.4 Incidence of the primary endpoint (RI/MI/Death) and its components at 48 hours, 7, and 30 days in the PRISM-PLUS trial".

	Tirofiban n=210	Tirofiban +Heparin n=213	Heparin n=211	p value (T vs H)[b]	p value and 95% C.I. (T+H vs H)[b]
Combined endpoint at 48 hours	16 (7.6%)	21 (9.9%)	17 (8.1%)	0.84 0.455, 1.893	0.57 0.621, 2.382
Combined endpoint at 7 days	38 (18.1%)	31 (14.5%)	32 (15.2%)	0.42 0.739, 2.074	0.87 0.559, 1.634
Combined endpoint at 30 days	50 (23.8%)	42 (19.7%)	38 (18.0%)	0.15 0.883, 2.279	0.67 0.683, 1.815
RIC at 48 hours	16 (7.6%)	20 (9.4%)	16 (7.6%)	0.99 0.483, 2.046	0.55 0.621, 2.460
RIC at 7 days	35 (16.7%)	29 (13.6%)	31 (14.7%)	0.57 0.688, 1.973	0.76 0.531, 1.589
RIC at 30 days	46 (21.9%)	36 (16.9%)	37 (17.5%)	0.26 0.813, 2.137	0.86 0.577, 1.586
MI (both fatal and non-fatal) at 48 hours	2 (1.0%)	3 (1.4%)	6 (2.8%)	0.19 0.067, 4.696	0.35 0.126, 2.095
MI (both fatal and non-fatal) at 7 days	12 (5.7%)	5 (2.4%)	13 (6.2%)	0.89 0.416, 2.134	0.063 0.127, 1.055
MI (both fatal and non-fatal) at 30 days	16 (7.6%)	10 (4.7%)	18 (8.5%)	0.74 0.439, 1.798	0.12 0.238, 1.181
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 0.971, 13.296	0.98 0.203, 5.128
Death at 30 days	11 (5.2%)	4 (1.9%)	4 (1.9%)	0.068 0.921, 9.456	0.98 0.250, 4.137
MI/Death at 48 hours	4 (1.9%)	4 (1.9%)	6 (2.8%)	0.55 0.187, 2.440	0.54 0.182, 2.468
MI/Death at 7 days	19 (9.0%)	8 (3.8%)	13 (6.2%)	0.24 0.742, 3.251	0.28 0.244, 1.496
MI/Death at 30 days	24 (11.4%)	14 (6.6%)	18 (8.5%)	0.31 0.732, 2.661	0.46 0.367, 1.577

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) 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.

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

Withdrawal of the tirofiban alone arm from the PRISM-PLUS trial (cont)

The DSMB was to use it's 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 death at 7 days in the PRISM-PLUS trial as of 11.15.95[a].

	Tirofiban n=314	Tirofiban +Heparin n=314	Heparin n=314	p value (T vs H)[b]	p value (T+H vs H)[b]
Death at 7 days	14 (4.5%)	**5 (1.6%)**	**4 (1.3%)**	**0.029** 1.177, 11.11	1.00 **0.334, 4.714**

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) and heparin (H).

Per the sponsor, these fmdings '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[c] 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%)[d]	5 (1.5%)	4 (1.1%)
Death at 30 days	21 (6.1%)[e]	7 (2.1%)	14 (4.0%)

a. Data from NDA 20-912. volume 1.59. tables 3. reference 57.

c. RIC: refractory ischemic conditions, including: (1) prolonged or repetitive anginal chest pain with ischemic ECG changes 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. 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.

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

Withdrawal of the tirofiban alone arm from the PRISM-PLUS trial (cont)

The final data for the deaths 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. 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. The deaths in the PRISM-PLUS trial, including the time course of the effect of tirofiban +heparin, tirofiban alone, and heparin alone on the incidence of death (figure 8.1.1.2d) is found in section 8.1.1 of the safety review.

Table 6.2.1.12.3.7 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.

Tertiary endpoint: **Angiographically** apparent thrombus

A tertiary endpoint of the PRISM-PLUS trial was the extent of angiographically apparent thrombus. The angiogram had to be p&formed within 96 hours. of starting the study (and so was still receiving study drug). The results quoted here are from the sponsor's analysis of the angiographic data.

The first endpoint of this analysis was the maximal extent of thrombus, graded on a 7-point scale. Subjects with grade 6 (chronic, complete obstruction) were excluded from the analysis. 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). Note that the tirofiban group has values that are quite similar to those in the heparin group.

Table 6.2.1.12.3.8 M imal extent of thr abus in culpri oronary lesion in PRISM-PLUS".

Outcome[b]	Tirofiban n=261	Tirofiban +Heparin n=608	Heparin n=622
0	132 (50.6%)	338 (55.6%)	314 (50.6%)
1	20 (7.7%)	71 (11.7%)	72 (11.6%)
2	33 (12.6%)	69 (11.4%)	56 (9.0%)
3	43 (16.5%)	69 (11.4%)	98 (15.8%)
4	11 (4.2%)	13 (2.1%)	19 (3.0%)
5	14 (5.4%)	22 (3.6%)	33 (5.3%)
6	8 (3.1%)	26 (4.3%)	30 (4.8%)

a. Data from NDA 20-912, volume 1. , reference. 5, table 22.
b. Thrombus grade: 0=absent; 1=possible; 2=small; 3=medium; 4=large; 5=recent total occlusion; 6=chronic total occlusion.

The second endpoint of this study was the TIMI flow past the culprit lesion (measured on a four point scale), which was identified by the primary investigators and then re-identified blindly by the central lab. Among the subjects with evaluable data, the flow was significantly greater in the tirofiban +heparin group than in the heparin group (odds reduction 35%, p=0.002). Flow was significantly improved in the tirofiban +heparin group, compared with the heparin group. Fewer of the combination group had diminished flow (TIMI grades 0,1,or 2) (18.1%) compared with the heparin group (25.5%).

Table 6.2.1.12.3.9 TIMI flow past culprit coronary lesion in the PRISM-PLUS trial[a].

Outcome[c]	Tirofiban n=243	Tirofiban +Heparin n=570	Heparin n=580
0	21 (8.6%)	44 (7.7%)	61 (10.5%)
1	2 (0.8%)	5 (0.9%)	11 (1.9%)
2	24 (9.9%)	54 (9.5%)	76 (13.1%)
3	196 (80.7%)	467 (81.9%)	432 (74.5%)

a. Data from NDA 20-912, volume 1.42. reference 5. table 22.
c. TIM flow: 0=no flow; 1=minimal perfusion; 2=partial perfusion; 3=complete perfusion.

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).

Other outcomes: cardiac procedures

A potential benefit of the use of tirofiban would be a reduction in the number of cardiac procedures performed during the acute period following an episode of NQWMIAJAP. The table below collects the number of cardiac procedures performed at any time during the PRISM-PLUS trial through day 30. It should be remembered that all subjects were to undergo angiography as part of the trial design. No trend towards fewer procedures was detected in the tirofiban +heparin group.

Table 6.2.1.12.3.10 Cardiac procedures during first 30 days of the PRISM-PLUS trial[a].

Procedure	Tirofiban n=334	Tirofiban +Heparin n=773	Heparin n=797	p value (T+H vs H)[b]
Any cardiac procedure	319 (92.5%)	708 (91.6%)	719 (90.2%)	0.38
Angiography	316 (91.6%)	704 (91.1%)	710 (89.1%)	0.21
Any revascularization	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
IABP	20 (5.8%)	36 (4.7%)	40 (5.0%)	0.81
# of procedures per subject (mean ±SD)	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).

Other outcomes: procedures & clinical events in subjects with 'Refractory Ischemic Conditions (RIC)'

The sponsor also performed an analysis of the subsequent cardiac procedures performed in subjects who had RIC. The definition of RIC is found in section 6.2.1.4, and includes subjects with cardiac ischemic symptoms resistant to medical therapy, subjects with hemodynamic instability, and those with frequent, repetitive angina/ischemia despite medical management.

The first analysis was performed on subjects who developed RIC 48 hours after starting the study (hence were by and large still taking the study drug infusion). Only 107/1915 of the entire subject population were included in this analysis (5.6%). Note that the primary endpoint could not be examined, as the development of RIC was part of the combination. In this analysis there were fewer revascularization procedures of any kind, and fewer CABGs in the combination group.

Table 6.2.1.12.3.11 Subsequent cardiac events and procedures performed in subjects with RIC developing within 3 hours of entry into the PRISM-PLUS trial".

Procedure/ Clinical event	Tirofiban n=23	Tirofiban +Heparin n=37	Heparin n=47
Death	4 (17.4%)	2 (5.4%)	4 (4.8%)
MI	8 (34.8%)	5 (13.5%)	11 (23.4%)
Death/MI	10 (43.5%)	5 (13.5%)	12 (25.5%)
Any cardiac procedure	22 (95.7%)	35 (94.6%)	46 (97.9%)
Angiography	22 (95.7%)	35 (94.6%)	45 (95.7%)
Any revascularization	16 (70%)	25 (67.6%)	42 (89.4%)
Angioplasty	10 (43.5%)	11 (29.7%)	16 (34.0%)
Atherectomy	0 (0%)	0 (0%)	2 (4.3%)
Stent	2 (8.7%)	4 (10.8%)	7 (14.9%)
CABG	7 (30.4%)	13 (35.1%)	23 (48.9%
IABP	4 (17.4%)	7 (18.9%)	11 (23.4%)

a. Data from NDA 20-912, volume 1.42, reference 5, table 23 and 28.

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

Other outcomes: procedures & clinical events in subjects RIC (cont)

Similarly, the sponsor reported the data for cardiac events and procedures for subjects developing RIC within 7 days of entry into the trial (hence; all finished with study drug infusion). Subjects who developed RIC in this group were at a high risk of requiring a cardiac procedure, but the rates of cardiac procedural events were similar in all groups.

Table 6.2.1.12.3.12 Subsequent cardiac events and procedures performed in subjects with RIC developing within days of entry into the PRISM-PLUS trial".

Procedure/ Clinical event	Tirofiban n=39	Tirofiban +Heparin n=72	Heparin n=101
Death	8 (20.5%)	11 (15.3%)	12 (11.9%)
MI	11 (28.2%)	9 (12.5%)	19 (18.8%)
Death/MI	17 (43.6%)	15 (20.8%)	26 (25.7%)
Any cardiac procedure	33 (43.6%)	61 (84.7%)	80 (79.2%)
Angiography	29 (74.4%)	50 (69.4%)	62 (61.4%)
Any revascularization	27 (69.2%)	47 (65.3%)	69 (68.3%)
IABP	8 (20.5%)	17 (23.6%)	17 (16.8%)

a. Data from NDA 20-912, volume 1.42, reference 5, table 29.

Other outcomes: analysis of primary endpoint according to the cardiac procedure received

The sponsor performed two further pre-specified analyses from the 48 hour and 7 day follow-up data, shown in the table below. 'Composite/procedures' is the composite of all deaths, myocardial infarctions, and those cases of refractory ischemia that occurred in subjects who also had a cardiac procedure performed (angiography, PTCA, stent placement, angioplasty, CABG, IABP, atherectomy). 'Composite/revascularization' is the composite of all deaths, all myocardial infarctions, and those cases of refractory ischemia that occurred in subjects who also had a revascularization procedure performed (angioplasty, CABG, atherectomy). In both groups, the tirofiban +heparin group had a lower incidence of the composite endpoint, compared with heparin alone.

Table 6.2.1.12.3.13 Incidence of two revised composite endpoints at 48 hours and 7 days in the PRISM-PLUS trial".

Endpoint	**Tirofiban n=345**	Tirofiban +Heparin **n=773**	Heparin **n=797**	Odds ratio **& 95%CI**	p value **(T+H vs H)[b]**
Composite/ Procedure at 48 hours[d]	25 (7.2%)	**42 (5.4%)**	59 **(7.4%)**	**0.696** 0.461, 1.049	**0.084**
Composite/ Procedure at 7 days	58 (16.8%)	95 **(12.3%)**	135 (16.9%)	0.669 **0.502,** 0.890	**0.006**
Composite/ Revasc. at 48 hours[e]	15 (4.4%)	28 **(3.6%)**	**47** (5.9%)	**0.581** 0.359, 0.940	**0.027**
Composite/ Revasc. at 7 days	47 (13.6%)	69 (8.9%)	**103** (12.9%)	**0.645** **0.466,** 0.892	0.008

a Data from NDA 20-9 12, volume 1.42, tables 17-20 and v ume 1.59, reference 55, table 1. Intent-to-treat population is used.
b. p value per the sponsor based on logistic regression analysis, comparing heparin (H) versus the combination (T +H)

Other outcomes: analysis of clinical events following PTCA during initial hospitalization

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). In the PRISM-PLUS, 2391773 (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. The demographics of the PTCA population in the PRISM-PLUS trial are summarized in Appendix 10, section 22.0. The efficacy of tirofiban in subgroups of the PRISM-PLUS trial is discussed further in the integrated efficacy summary, section 7.0.3.3 and 7.0.3.3.

Clinical outcomes in the 30 days after PTCA

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, 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.

The sponsor also performed an analysis of the time course of the effect of tirofiban and heparin on the primary endpoint and its components. The first two figure show the time course of the occurrence of the primary endpoint out to 30 days, and then out to 180 days.

Table 6.2.1.12.3.14 Clinical events during the first 30 days grouped according to receipt of PTCA in the PRISM-PLUS trial[a].

Procedure	Tirofiban	Tirofiban +Heparin	Heparin
Composite Endpoint (RIC, MI, Death)			
All subjects	81/345 (23.5%)	143/773 (18.5%)	178/797 (22.3%)
Subjects who underwent PTCA[b]	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%)
MI (fatal/ nonfatal)			
All subjects	31/345 (9.0%)	51/773 (6.6%)	73/797 (9.2%)
Subjects who underwent PTCA[b]	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%)
Death			
All subjects	21/345 (6.1%)	28/773 (3.6%)	36/797 (4.5%)
Subjects who underwent PTCA[b]	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 FDA.

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

Clinical outcomes in the 7 days after 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 3 1.6%, 95% CI 11.7% to 47%, p=0.004) in this population.

Table 6.2.1.12.3.15 Clinical events during the first 7 days following receipt of PTCA in the PRISM-PLUS tri

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.

Clinical outcomes for subjects who underwent PTCA while receiving study drug

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 the total tirofiban group, 19.9% of the total tirofiban +heparin group, and 2 1.8% of the total 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 6.2.1.12.3.16 PRISM-PLUS subjects who received PTCA[a].

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 those subjects who received PTCA 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). 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 6.2.1.12.3.17 Clinical event subsequent to PTCA in PRISM-PLUS subjects who underwent PTCA while on study drug".

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.

Pre-specified subgroup analyses

The results at the end of 7 days (the time of the pre-specified primary endpoint) were also analyzed for interactions with several subgroups, and the results are shown below. Overall, subjects receiving tirofiban +heparin had a lower incidence rate of the primary endpoint (death, MI, RIC) than the subjects in the heparin group.

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.

Table 6.2.1.12.3.18 Incidence of the combined endpoint and its components at 7 days in the PRISM-PLUS trial".

Subgroup	Tirofiban	Tirofiban +Heparin	Heparin
Age			
<65	18/176 (10.2%)	34/402 (8.5%)	50/402 (12.4%)
≥65	41/169 (24.3%)	66/371 (17.8%)	93/395 (23.5%)
Gender			
Female	28/114 (24.6%)	34/254 (13.4%)	48/252 (19.0%)
Male	31/231 (13.4%)	66/519 (12.7%)	95/545 (17.4%)
Race			
Caucasian	55/312 (17.6%)	92/664 (13.9%)	126/675 (18.7%)
Other	4/33 (12.1%)	8/109 (7.3%)	17/ 122 (13.9%)
Heparin use before trial entry			
Yes	42/230 (18.3%)	73/506 (14.4%)	102/501 (20.4%)
No	17/115 (14.8%)	27/267 (10.1%)	41/296 (13.8%)
Aspirin before trial entry			
Yes	37/184 (20.1%)	65/406 (16.0%)	96/408 (23.5%)
	22/161 (13.7%)	35/367 (9.5%)	47/389 (12.1%)
Beta-blocker before trial entry			
Yes	41/166 (24.7%)	55/422 (13.0%)	971422 (23.5%)
No	181179 (10.1%)	45/351 (12.8%)	46/375 (12.3%)
Calcium channel blocker before trial entry			
Yes	20/149 (19.5%)	59/330 (17.9%)	77/307 (25.1%)
No	30/196 (15.3%)	41/443 (9.3%)	66/490 (13.5%)
ECG evidence of ischemia			
S-T depression	44/196 (22.4%)	73/440 (16.6%)	104/479 (21.7%)
S-T elevation	8/45 (17.8%)	8/104 (7.7%)	16/92 (17.4%)
T-wave inversion	4/79 (5.1%)	14/156 (9.0%)	12/146 (8.2%)
NQWMI			
Possible	14/117 (12.0%)	26/239 (10.9%)	46/271 (17.0%)
Evolving	8/40 (20.0%)	13/106 (12.3%)	19/98 (19.4%)
Unstable angina	37/188 (19.7%)	61/428 (14.2%)	781428 (18.2%)
Diabetes			
Yes	12184 (14.3%)	25/169 (14.8%)	42/193 (21.8%)
Smoking			
Never	24/100 (24.0%)	35/225 (15.6%)	591251 (23.5%)
Ex-smoker	24/138 (17.4%)	42/290 (14.5%)	571292 (19.5%)
Current smoker	11/107 (10.3%)	22/255 (8.6%)'	25/245 (10.2%)

Data from NDA 20-912, volume 1.55, re 1, tables 24. Intent-to-treat population is used. NA= not applicable