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CLINICAL PHARMACOLOGY REVIEW

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INTRODUCTION

This medical review of NDA 20-912 represents a detailed examination of pharmacokinetic and pharmacodynamic as well as safety data on Tirofiban, an antagonist of the GP IIb/IIIa receptor, from the following clinical pharmacology studies: protocols # 001, 002, 004, 009, 012, and 014.

INDIVIDUAL CLINICAL STUDY REPORTS

PROTOCOL NO.: 001

PROTOCOL TITLE: A Two-Part Dose-Escalation Study Of One- And Four-Hours Intravenous Infusions Of MK-0383 (Tirofiban) In Healthy, Male Subjects: A Double-Blind, Placebo-Controlled, Parallel Group Study Of Safety, Tolerability And Activity.

This study essentially was an exploratory dose-finding pharmacology investigation of the inhibitory effect of Tirofiban on platelet aggregation.

STUDY DESIGN: This was a randomized, double-blind, placebo-controlled, parallel group, dose-escalation¹, two-part, 1- and 4-hour intravenous infusion, study in 44 healthy male volunteers designed to determine the safety, tolerability and inhibition of platelet aggregation of Tirofiban. Subjects were monitored for adverse events throughout the study. Measurement of hematology, blood chemistry, and urinalysis parameters, before the study and after each treatment, also aided in the assessment of the safety of Tirofiban administration.

The objectives of the study were: 1) to determine the safety and tolerance of Tirofiban when given by constant infusion for 1- and 4-hours within the dose range of 0.05 to 16.0 µg/kg/min; and 2) to determine the relationship between Tirofiban infusion rates and inhibition of platelet aggregation.

RESULTS: Forty-four healthy Caucasian males from 20 to 28 years of age were enrolled in the study. Twenty-four subjects participated in the first part (1-hour infusion) of this study and 20 in the second part (4-hour infusion). The disposition of subjects/dose level of Tirofiban is summarized in Table 1. No subjects discontinued due to a clinical or laboratory adverse event.

Table 1. Disposition Of Subjects/Dose

	No. Of Subjects	Dose (µg/kg/min)
1-Hour Infusion	6	Placebo
	3	.05
	3	.10
	3	.15
	6	.25
	3	.40
4-Hour Infusion	5	Placebo
	3	.10
	9	.15
	3	.20

[Adapted from NDA 20-912, Volume 38, Table 4, page 16.]

The pharmacokinetics of Tirofiban are described next. Mean plasma concentration-time profiles of Tirofiban for each of the five dose groups after 1-hour i.v. infusion are shown in Figure 1. And the corresponding means AUC₀₋₂₄₀ for the 1-hour infusions are given in Table 2. Mean plasma concentration and AUC₀₋₂₄₀ appear to increase in a dose-related manner.

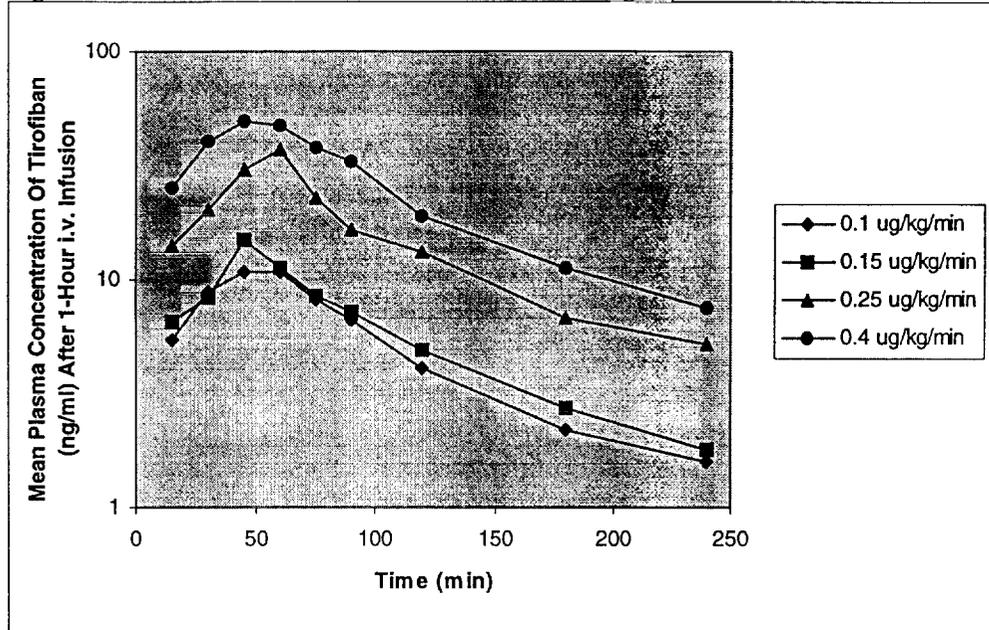
¹ Dose advancement to be stopped based on achievement of targeted levels of platelet inhibition i.e., 2.5-fold prolongation of bleeding time.

Table 2. Summary Of Mean (\pm SD) AUC₀₋₂₄₀ After 1-Hour Infusion Of Tirofiban By Dose

Variable	0.05 $\mu\text{g}/\text{kg}/\text{min}$ N=3	0.10 $\mu\text{g}/\text{kg}/\text{min}$ N=3	0.15 $\mu\text{g}/\text{kg}/\text{min}$ N=3	0.25 $\mu\text{g}/\text{kg}/\text{min}$ N=6	0.40 $\mu\text{g}/\text{kg}/\text{min}$ N=3
AUC ₀₋₂₄₀ (ng·min/mL) ^a	755.7 \pm 178.4	1175.5 \pm 131.6	1366.7 \pm 247.7	3270.4 \pm 1047.9	5537.0 \pm 958.2

[Sponsor's analysis. Adapted from NDA 20-912, Volume 38, Table 6, page 29. ^aExpressed in terms of the HCL salt.]

Figure 1. Mean Plasma Concentration Of Tirofiban (ng/ml) After 1-Hour Intravenous Infusion



[Sponsor's analysis. Adapted from NDA 20-912, Volume 38, Tables 3, 4, 5, & 6, pages 114-117.]

Pharmacokinetic parameters of Tirofiban after 4-hour i.v. infusion are summarized in Table 3. The mean terminal half-life of Tirofiban was 1.67 hours. Systemic clearance (CL_s) does not seem to be influenced by dose across the range infused in this study.

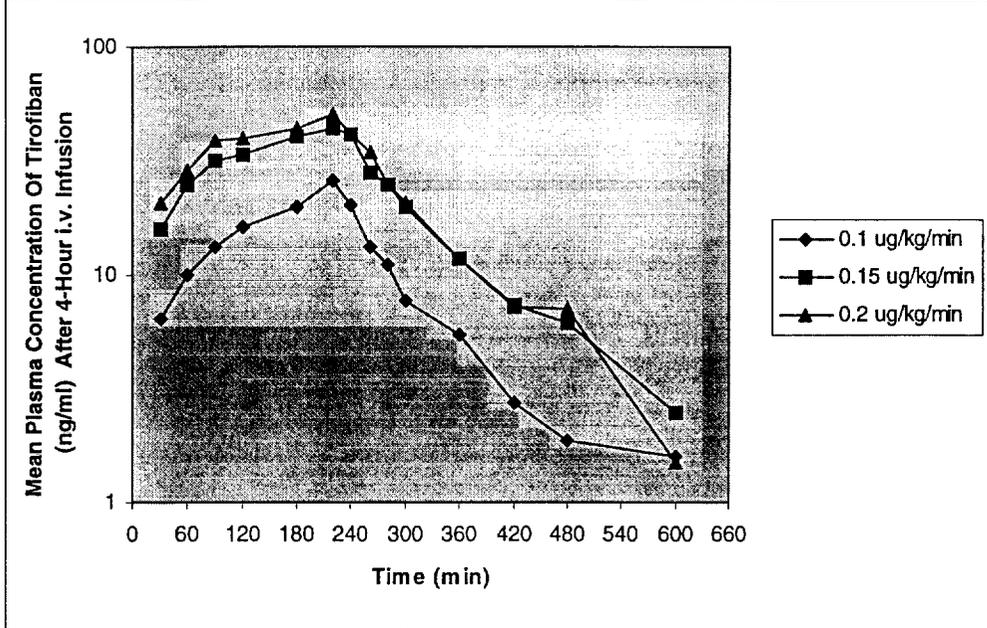
Table 3. Summary Of Mean (\pm SD) Pharmacokinetic Parameters After 4-Hour Infusion Of Tirofiban By Dose

Variable	0.10 $\mu\text{g}/\text{kg}/\text{min}$ N=3	0.15 $\mu\text{g}/\text{kg}/\text{min}$ N=9	0.20 $\mu\text{g}/\text{kg}/\text{min}$ N=3	All Doses N=15
CL_s (mL/min)	336.6 \pm 66.2	270.2 \pm 103.8	265.2 \pm 33.0	282.5 \pm 87.9
$t_{1/2}$ (hr)	2.38 \pm 1.26	1.6 \pm 0.21	1.14 \pm 0.16	1.67 \pm 0.65
AUC _{0-t} (ng·min/mL) ^a	5350.3 \pm 1076.2	11497.1 \pm 3901.0	12729.5 \pm 1462.0	10514.2 \pm 4068.6
AUC _∞ (ng·min/mL) ^a	5645.2 \pm 1020.6	11838.0 \pm 4026.3	12880.1 \pm 1508.6	10807.9 \pm 4129.3
Vd _{ss} (L)	43.2 \pm 11.8	27.3 \pm 7.3	24.5 \pm 2.2	29.9 \pm 9.9

[FDA's analysis. Adapted from NDA 20-912, Volume 38, Table 4, page 101. ^aExpressed in terms of the HCL salt.]

The mean plasma concentration of Tirofiban after 4-hour i.v. infusion for each dose is depicted in Figure 2. Data shown in this figure suggest that steady state was not reached by the end of the 4-hour administration.

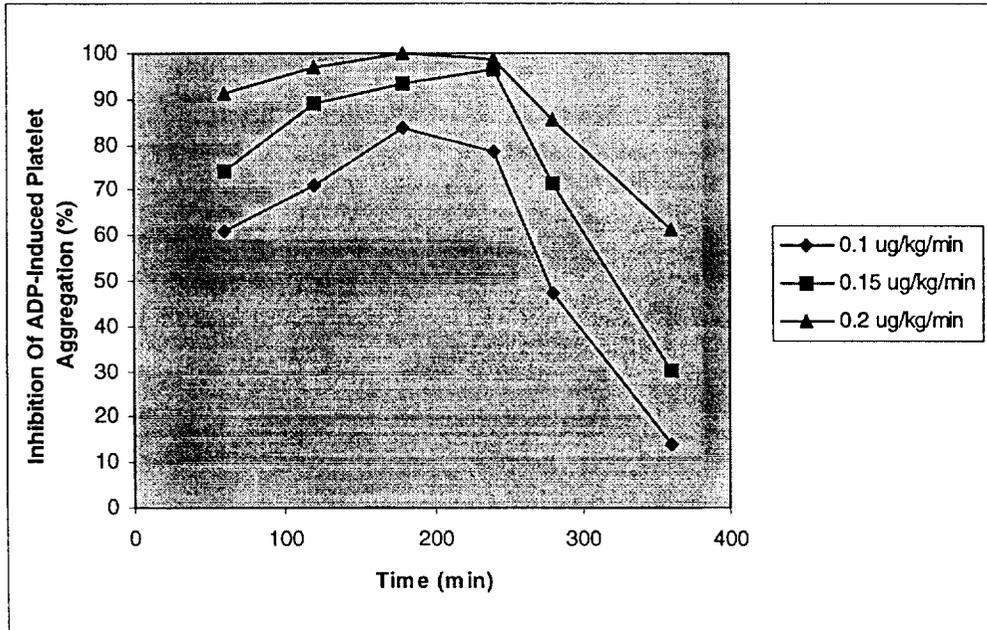
Figure 2. Mean Plasma Concentration Of Tirofiban (ng/ml) After 4-Hour Intravenous Infusion



[Sponsor's analysis. Adapted from NDA 20-912, Volume 38, Tables 7, 8, & 9, pages 118-120.]

Mean inhibition of ADP-induced platelet aggregation (%) after 4-hour intravenous infusion of Tirofiban is depicted in Figure 3. Tirofiban appears to inhibit ADP-induced platelet aggregation in a dose-dependent manner (Figures 3 & 4).

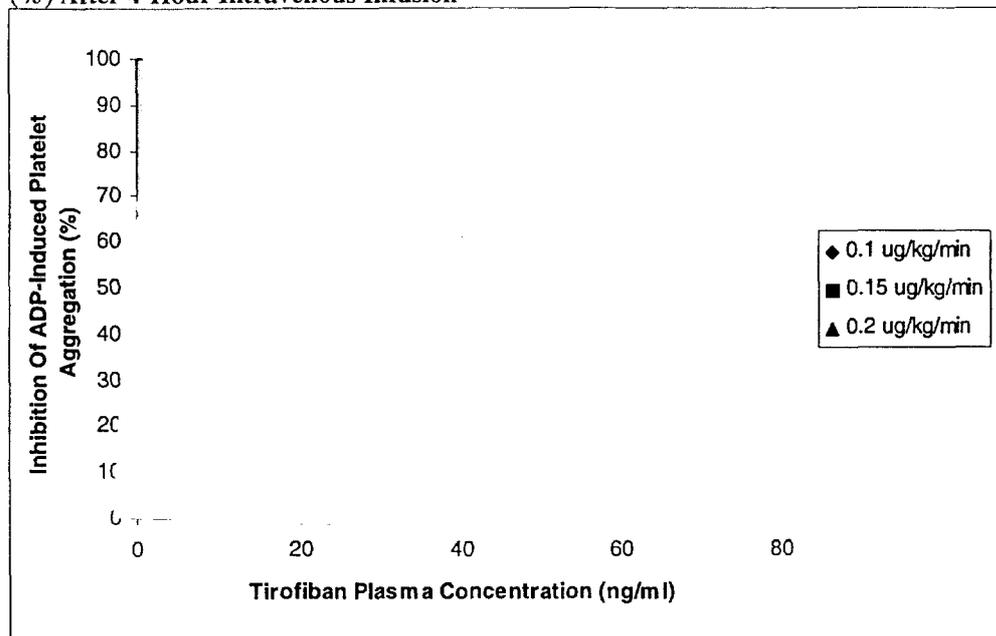
Figure 3. Mean Inhibition Of ADP-Induced Platelet Aggregation (%) After 4-Hour Intravenous Infusion Of Tirofiban



FDA's analysis. Adapted from NDA 20-912, Volume 38, Tables 5, pages 102-103.]

Pharmacodynamic analysis of the individual Tirofiban plasma concentration-inhibition of ADP-induced platelet aggregation profiles after the 4-hour i.v. infusion is illustrated in Figure 4.

Figure 4. Tirofiban Plasma Concentration (ng/ml) Versus Inhibition Of ADP-Induced Platelet Aggregation (%) After 4-Hour Intravenous Infusion



[Sponsor's analysis. Adapted from NDA 20-912, Volume 38, Tables 5, pages 102-103.]

SAFETY: No subject/patient had a serious adverse event or discontinued due to a clinical adverse experience. According to the sponsor "no clinically important changes between prestudy and poststudy physical examinations, ECGs were noted." Similarly, no clinically significant changes from baseline were noted for blood pressure and pulse rate, and laboratory parameters.

CONCLUSIONS: In this study Tirofiban was well tolerated in healthy male subjects. Tirofiban has a short half-life ~1.5 hours, its systemic clearance is not affected by the dosing range used in this study. Tirofiban inhibits ADP-induced platelet aggregation and prolongs bleeding time in a dose-dependent manner.

PROTOCOL NO.: 002

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Three-Period Crossover Study Of A Four-Hour Intravenous Infusion Of MK-0383 (Tirofiban) With And Without Aspirin Pretreatment In Healthy Male Subjects

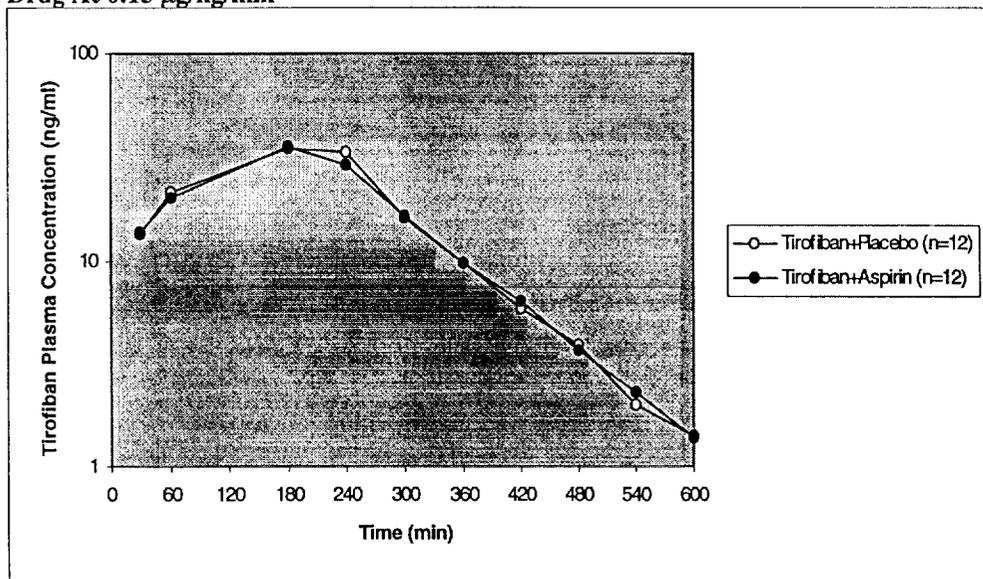
Inasmuch as patients treated with Tirofiban may also received aspirin therapy, defining the safety, tolerability and degree of interaction, if any, between these two drugs became an important part of the developmental program of Tirofiban. This study specifically addressed that issue.

STUDY DESIGN: This was a randomized, three-period, placebo-controlled, crossover², double-blind, drug interaction study. Twelve healthy male volunteers were enrolled and received all 3 treatments³. The objectives of the study were: 1)to assess the safety and tolerability of Tirofiban during a 4-hour continuous infusion at the dose of 0.15 µg/kg/min, with and without pretreatment with oral aspirin; 2)to determine if plasma concentrations of Tirofiban are altered by aspirin; 3)to determine if the inhibition of platelet function produced at end-infusion of an “active dose” of Tirofiban is altered by aspirin; 4)to determine, in a preliminary manner, if the inhibition of platelet function produced during the approach to steady state and the elimination phases of the Tirofiban infusion are altered by aspirin; and 5)to determine the inhibition of platelet function produced by the dose regimen of aspirin used in this study.

Plasma and urinary measurements of Tirofiban were attained, and pharmacokinetic and pharmacodynamic analyses of the results were performed. Platelet function and its degree of inhibition was also determined. Subjects were monitored for adverse events throughout the study. Measurement of hematology, blood chemistry, and urinalysis parameters, before and after Tirofiban administration, were carried out to assess the safety of Tirofiban.

RESULTS: All twelve healthy male subjects, 19 to 28 years of age, who were enrolled completed the study. Mean plasma concentrations of Tirofiban with and without aspirin pretreatment were similar (Figure 5).

Figure 5. Mean Concentrations Of Tirofiban In Plasma Of Subjects Receiving A 4-Hour I.V. Infusion Of Drug At 0.15 µg/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 39, Table 2, page 831.]

² A washout period of at least 14 days separated each of the treatments.

³ According to a randomized allocation schedule, on each study day at least 1 subject received Tirofiban with aspirin pretreatment, Tirofiban with placebo, and a placebo infusion with aspirin pretreatment.

Pharmacokinetic parameters did not differ for Tirofiban when given alone or following aspirin administration (325 mg orally at approximately 3 p.m. on Day -1 and ~1 hour prior to Tirofiban dosing; Table 4). Thus, the results suggest that aspirin pretreatment does not significantly modify the pharmacokinetics of Tirofiban when administered as a four-hour i.v. infusion.

Table 4. Summary Of Mean (\pm SD) Pharmacokinetic Parameters In Healthy Male Subjects Receiving 0.15 μ g/kg/min I.V. Infusions Of Tirofiban For 4-Hours, With And Without Aspirin Pretreatment

Variable	Tirofiban+Placebo N=12	Tirofiban+Aspirin N=12
CL (mL/min)	314.36 \pm 64.64	337.86 \pm 106.09
CL _r (mL/min)	121.63 \pm 24.86	120.74 \pm 33.00
CL _{nr} (mL/min)	192.73 \pm 53.54	217.12 \pm 81.83
t _{1/2} (hr) ^a	1.44 \pm 0.27	1.47 \pm 0.28
λ (hr ⁻¹)	0.4825 \pm 0.0889	0.4714 \pm 0.0904
C _{4hr} (ng/mL)	33.44 \pm 5.49	29.23 \pm 9.54
AUC _T (ng·hr/mL)	155.07 \pm 24.91	152.25 \pm 44.03
AUC _∞ (ng·hr/mL)	158.61 \pm 25.32	156.55 \pm 44.87
Vd _{ss} (L)	32.36 \pm 6.87	35.90 \pm 11.64
Urinary Recovery _{0-24 hr} (μg)	1148.98 \pm 193.21	1094.30 \pm 226.99
Urinary Recovery _{0-24 hr} (% dose) ^b	40.16 \pm 8.76	37.33 \pm 7.19

[Sponsor's analysis. Adapted from NDA 20-912, Volume 39, Table 3, pages 812 & 813. ^aHarmonic mean and pseudo SD. ^bn=11.]

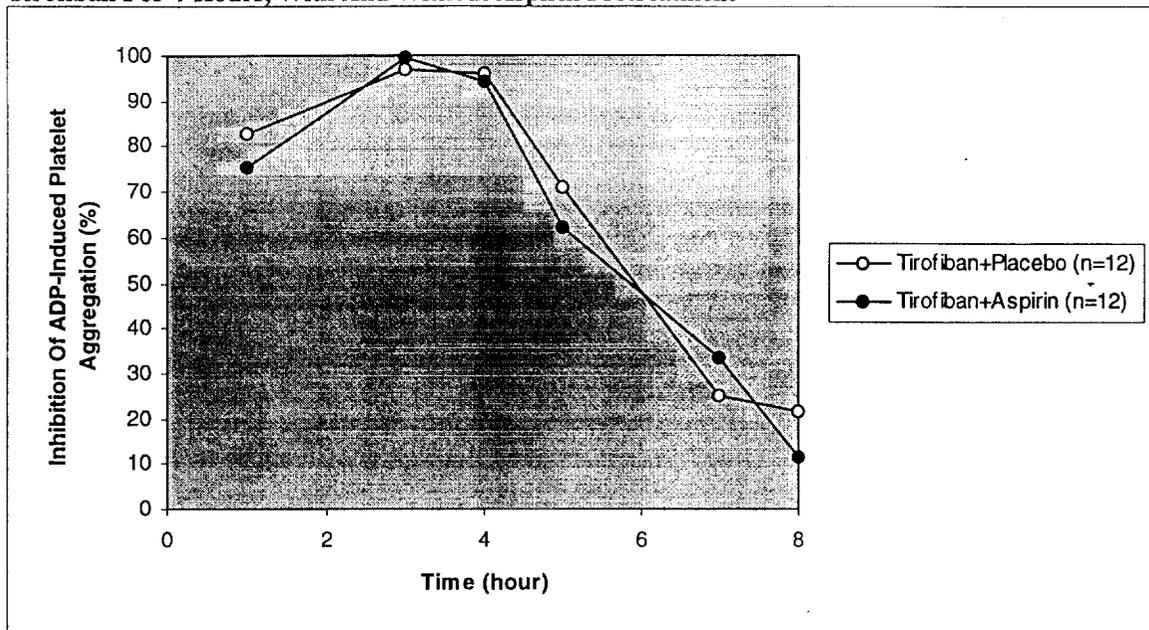
Inhibition of ADP-induced platelet aggregation by Tirofiban does not appear to be significantly influenced by aspirin pretreatment (Table 5 and Figure 6). The mean (\pm SD) C₅₀ free base was 9.5 \pm 5.3 mg/mL for Tirofiban+Placebo and 9.5 \pm 3.1 mg/mL for Tirofiban+Aspirin.

Table 5. Mean (\pm SD) Inhibition Of ADP-Induced Platelet Aggregation (%) After 0.15 μ g/kg/min I.V. Infusions Of Tirofiban For 4-Hours, With And Without Aspirin Pretreatment

Time (hour)	Tirofiban+Placebo N=12	Tirofiban+Aspirin N=12
1	82.68 \pm 8.35	75.22 \pm 17.19
3	97.12 \pm 4.87	99.60 \pm 1.31 ^c
4	96.00 \pm 6.08	94.06 \pm 5.67
5	70.78 \pm 23.05 ^a	61.99 \pm 27.61 ^d
7	25.30 \pm 22.41	33.39 \pm 16.90
8	21.78 \pm 17.31 ^b	11.56 \pm 12.01 ^c

[Sponsor's analysis. Adapted from NDA 20-912, Volume 39, Table B-1, page 826. ^an=11. ^bn=4. ^cn=11. ^dn=10. ^en=11]

Figure 6. Mean Inhibition Of ADP-Induced Platelet Aggregation (%) After 0.15 µg/kg/min I.V. Infusions Of Tirofiban For 4-Hours, With And Without Aspirin Pretreatment



[Sponsor's analysis. Adapted from NDA 20-912, Volume 39, Table B-1, page 826.]

The effect of Tirofiban, with and without aspirin pretreatment, on bleeding time is summarized in Table 6. Albeit the numerical differences documented for the changes in bleeding time among the groups are not statistically significant, the data is suggestive of an additive effect of aspirin pretreatment on Tirofiban's activity.

Table 6. Summary Of Mean^a (±SD) Bleeding Time (min) By Treatment

Time	Tirofiban+Placebo (n=12)	Tirofiban+Aspirin (n=12)	Aspirin+Placebo (n=12)
Day -1	5.0±0.7 ^b	5.1±0.8	5.5±0.9 ^b
Preinfusion	5.8±0.8	8.4±2.1	9.4±2.0
220 Minutes	11.2±2.5	21.1±5.8	10.3±1.8

[Sponsor's analysis. Adapted from NDA 20-912, Volume 39, Table 8, page 767. ^aGeometric mean. Aspirin+Placebo significantly different from Tirofiban+Placebo at baseline (Day -1), p<0.05.]

SAFETY: All the twelve subjects enrolled completed the study. Only two subjects experienced an adverse event. Subject AN 004 had a nose bleed on day 3rd of treatment (Tirofiban+Aspirin), 50 minutes after the infusion was terminated. Another subject, AN 011, developed nausea and vomiting during the second day of treatment (Tirofiban+Aspirin), 9¼ hours after the infusion was discontinued. Only in one subject an abnormal laboratory value was reported. Subject AN 002 had a positive stool guaiac test at the discharge examination on the 3rd treatment day (Aspirin+Placebo).

Three subjects had ECGs abnormalities. Subject AN 001 had a sinus arrhythmia at predose on the 2nd treatment day (Aspirin+Placebo) and at predose on the 3rd treatment day (Placebo+Tirofiban). Subject AN 003 developed a sinus arrhythmia at prestudy, and subject AN 012 had a sinus bradychardia prior to discharge on the 3rd treatment day (Aspirin+Tirofiban).

Analyses of changes in vital signs demonstrated a statistically significant increase in temperature (0.3°C) from the preinfusion value for Aspirin+Placebo and Placebo+Tirofiban periods. However, there were no significant between-treatment differences in these increases. No changes in the respiration were noted. Except for statistically significant decreases in diastolic blood pressure with Aspirin+Placebo at 480 minutes and at discharge (3.7 mmHg) pulse rate

and blood pressure measurements remained fairly constant throughout the study. Of note, there were no significant between-treatment differences at this time point.

No clinically significant changes in laboratory parameters were observed.

CONCLUSIONS: Although no serious adverse experiences were reported, a patient on Tirofiban+Aspirin had a nose bleed.

Aspirin pretreatment does not appear to modify the pharmacokinetics of Tirofiban. Although, aspirin pretreatment does not appear to affect the inhibitory effect of Tirofiban on ADP-induced platelet aggregation, bleeding time is further prolonged by Tirofiban in the presence of aspirin pretreatment.

PROTOCOL NO.: 004

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Pilot Study To Investigate The Safety, Tolerability, Pharmacokinetics And Pharmacodynamics Of A Sustained Infusion Of MK-0383 (Tirofiban) In Patients With Stable Coronary Artery Disease

The sponsor defended the need to explore the safety, tolerability, pharmacokinetics and pharmacodynamics of a sustained Tirofiban i.v. infusion in patients with stable coronary artery disease because this group of patients is "demographically similar to the one that would ultimately receive the drug in the clinical setting."

STUDY DESIGN: This was a multicenter, randomized (1:1 ratio), double-blind, placebo-controlled pilot study in twenty-four patients with stable coronary artery disease (CAD). Tirofiban or matching placebo was administered intravenously at a rate of 0.3 µg/kg/min for 30 minutes followed by 5.5-hour sustained infusion at 0.075 µg/kg/min. Patients were stratified based on their prior aspirin usage⁴. Patients were monitored for adverse events throughout the study. Measurement of hematology, blood chemistry, and urinalysis parameters, before, during and after Tirofiban administration, were carried out to assess its safety.

Relevant pharmacokinetic parameters measured included systemic clearance (CL), renal clearance (CL_r), terminal half-life (t_{1/2}), elimination rate constant (λ), volume of distribution at steady state (Vd_{SS}), and 24-hour urinary recovery.

The objectives of this study were three-fold: 1) to assess the safety and tolerability of Tirofiban; 2) to determine the degree of inhibition of ADP-induced platelet aggregation in the presence or absence of aspirin; and 3) to determine the pharmacokinetics of Tirofiban during sustained i.v. infusion in patients with stable coronary artery disease.

The primary efficacy variables assessed were percent inhibition of ADP-induced platelet aggregation and extension of template bleeding time⁵ during the sustained infusion of Tirofiban.

RESULTS: Of the 24 patients randomized to the study all were Caucasian and only two were female. Mean age was 58.4 years with a range of 46 to 72 years, and the average duration of coronary artery disease was 3 years and 11 months. The most common secondary diagnosis included hypertension and hyperlipidemia, as well as history of coronary bypass surgery, percutaneous transluminal coronary angioplasty and myocardial infarction.

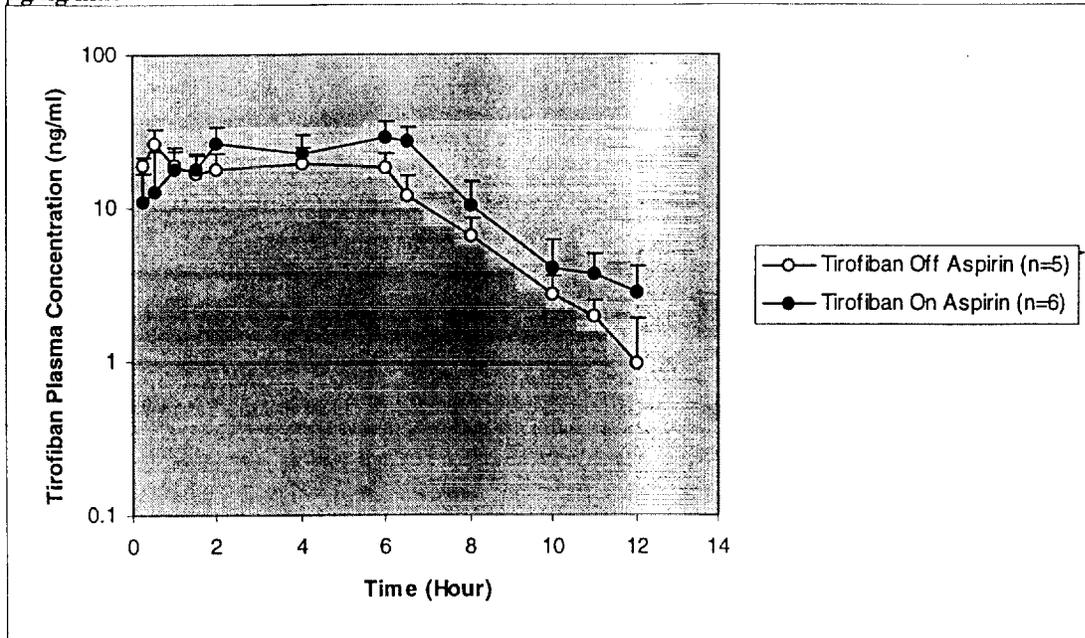
Twenty-three patients completed the study (i.e., the 6-hour drug infusion period). Patient AN 0021, receiving Tirofiban alone, was discontinued because of thrombocytopenia, and another patient (AN 0022) requested to be withdrawn after hour 6 of the study.

Results from the analyses of pharmacokinetic and pharmacodynamic variables are described next. Figure 7 depicts the mean (±SD) Tirofiban plasma concentration-time profiles from patients who were both on and off aspirin. Patients who had received aspirin appear to have slightly lower plasma concentrations across the duration of the maintenance phase. According to the sponsor, the noted numerical difference did not reach statistical significance.

⁴ Patients were assigned to one of two panels: panel 1 if they had not ingested aspirin within 7 days prior to randomization; panel 2 if they had ingested aspirin within 7 days prior to randomization. Patients in this panel took 325 mg of aspirin at 22 to 26 hours prior and again at 2 hours prior to the administration of Tirofiban/Placebo.

⁵ Bleeding time (BT) extension was determined by the following formula: BT time point/BT baseline.

Figure 7. Mean (\pm SD) Concentrations Of Tirofiban In Plasma Of CAD Patients Off And On Aspirin Following 30-Minute I.V. Infusion At 0.3 μ g/kg/min Followed By 5.5-Hour Sustained I.V. Infusion At 0.075 μ g/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 40, Table 5, page 1661.]

A summary of the examined pharmacokinetic variables is provided in Table 7. According to the sponsor, the differences observed for the listed variables were not statistically significant between the groups.

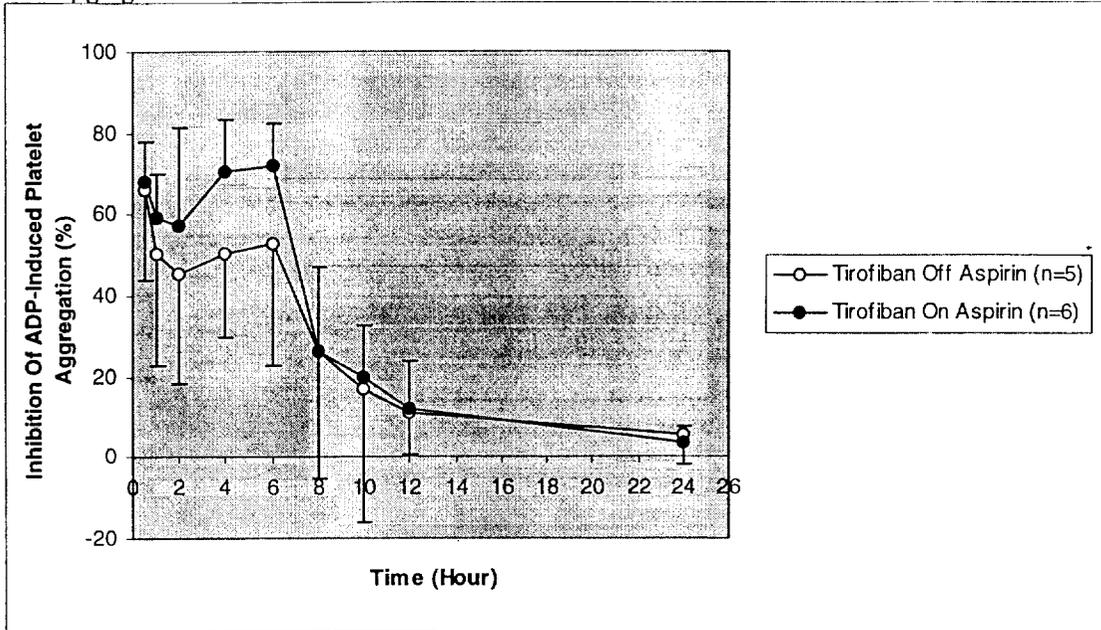
Table 7. Summary Of Mean^a (\pm SD) Pharmacokinetic Parameters Of Tirofiban In CAD Patients

Variable	Off-Aspirin N=5	On-Aspirin N=6
CL (mL/min)	307.96 \pm 49.47	232.24 \pm 57.15
CL _r (mL/min)	104.60 \pm 21.51	98.57 \pm 36.70
t _{1/2} (hr)	1.74 \pm 0.26	2.0 \pm 0.30
AUC _∞ (ng·hr/mL)	149.29 \pm 37.56	241.59 \pm 55.0
Vd _{ss} (L)	43.01 \pm 8.13	41.32 \pm 13.09
Urinary Recovery _{0-24 hr} (% dose)	34.70 \pm 5.15	44.01 \pm 9.27

[Sponsor's analysis. Adapted from NDA 20-912, Volume 40, Table 3, page 1659. ^aArithmetic mean.]

Figure 8 delineates the inhibition of ADP-induced platelet aggregation profiles for Tirofiban-treated patients on/off aspirin. It does appear that coadministration of aspirin may enhance the inhibition of ADP-induced platelet aggregation produced by a sustained infusion (i.e., 6 hours) of Tirofiban.

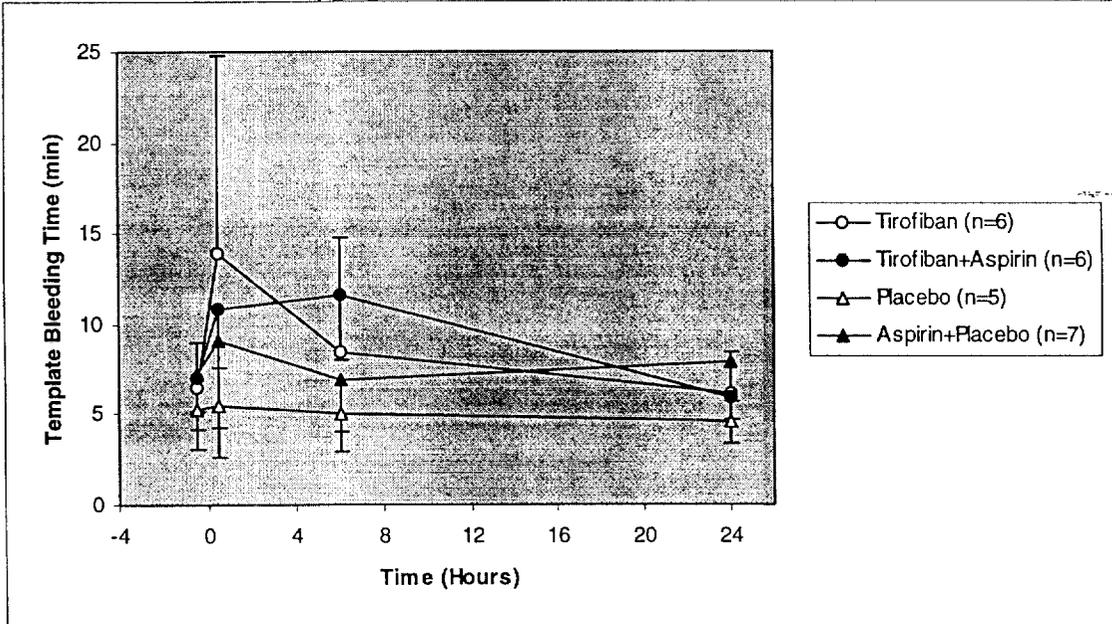
Figure 8. Mean (\pm SD) Inhibition Of ADP-Induced Platelet Aggregation (%) In CAD Patients Off And On Aspirin Following 30-Minute I.V. Infusion At 0.3 μ g/kg/min Followed By 5.5-Hour Sustained I.V. Infusion At 0.075 μ g/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 40, Table 4, page 1660.]

The results on bleeding time are illustrated in Figure 9. The presence of aspirin may slightly enhance the effect of Tirofiban on bleeding time.

Figure 9. Mean (\pm SD) Template Bleeding Time (min) In CAD Patients Off And On Aspirin Following 30-Minute I.V. Infusion At 0.3 μ g/kg/min Followed By 5.5-Hour Sustained I.V. Infusion At 0.075 μ g/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 40, Appendix 4.1.7, page 1852.]

SAFETY: The safety analysis includes all the twenty-four patients who entered the study. Patient AN 0021 was discontinued from the study because of thrombocytopenia⁶, abnormality that developed within 2 hours of Tirofiban infusion. Another patient (AN 0004) had 1 to 2 RBCs in the urine 24 hours after the i.v. placebo infusion was started.

Of note, there were no physical exam or vital sign adverse experiences reported or clinically significant deviations in serum chemistries during the study infusion period.

CONCLUSIONS: Of concern one patient was discontinued from the study due to thrombocytopenia.

Pharmacokinetic and pharmacodynamic results from these patients with CAD are in keeping with what is known about the clinical pharmacology of Tirofiban in healthy subjects off/on aspirin.

⁶ Platelet counts for AN 0021 are summarized in NDA 20-912, Volume 39, Table 12, page 1363.

PROTOCOL NO.: 009**PROTOCOL TITLE: An Open-Label, One-Hour I.V. Infusion Study To Determine The Influence Of Hepatic Insufficiency On The Pharmacokinetics Of MK-0383 (Tirofiban)**

Because Tirofiban seems to be partly excreted unchanged by the liver and the kidney, and it may be given to patients with hepatic insufficiency, the sponsor sought to define the pharmacokinetics of Tirofiban in hepatically impaired patients to support dosing recommendations.

STUDY DESIGN: This was an open, one-period, pharmacokinetic study conducted in 12 patients with hepatic insufficiency who had Pugh Child's modified score of 5 to 11, and 12 healthy subjects. Subjects and patients received an i.v. infusion of Tirofiban (0.10 µg/kg/min for 1 hour). Safety was evaluated by monitoring subjects and patients for clinical and laboratory adverse events.

The objectives of this study were: 1) to determine the pharmacokinetics of a Tirofiban i.v. infusion dose (0.10 µg/kg/min for 1 hour) in patients with hepatic insufficiency; 2) to compare systemic clearance of Tirofiban in patients with hepatic insufficiency to that in normal volunteers; 3) to assess the tolerability of a 1-hour i.v. infusion dose of Tirofiban in patients with hepatic insufficiency; and 4) to investigate the effect of Tirofiban on platelet aggregation in patients with hepatic insufficiency in relation to similar data in healthy subjects.

RESULTS: Twelve healthy subjects, between the ages of 38 and 62, entered the study, one was Asian the rest were Caucasian and only 2 of them were female. All twelve patients, between the ages of 42 and 65, participating in the study had cirrhosis and a Pugh Child's modified score ≥5, were Caucasian, and two of them were female. No subject/patient discontinued the study.

Pharmacokinetics of Tirofiban in healthy subjects and patients with hepatic insufficiency are described in Table 8. Of note, there was a significant difference between the means of the hepatic patients and healthy subjects for the volume of distribution of Tirofiban (p<0.013). The nonrenal clearance of Tirofiban was numerically lower in hepatic patients than in healthy subjects, however there was no significant difference between the means.

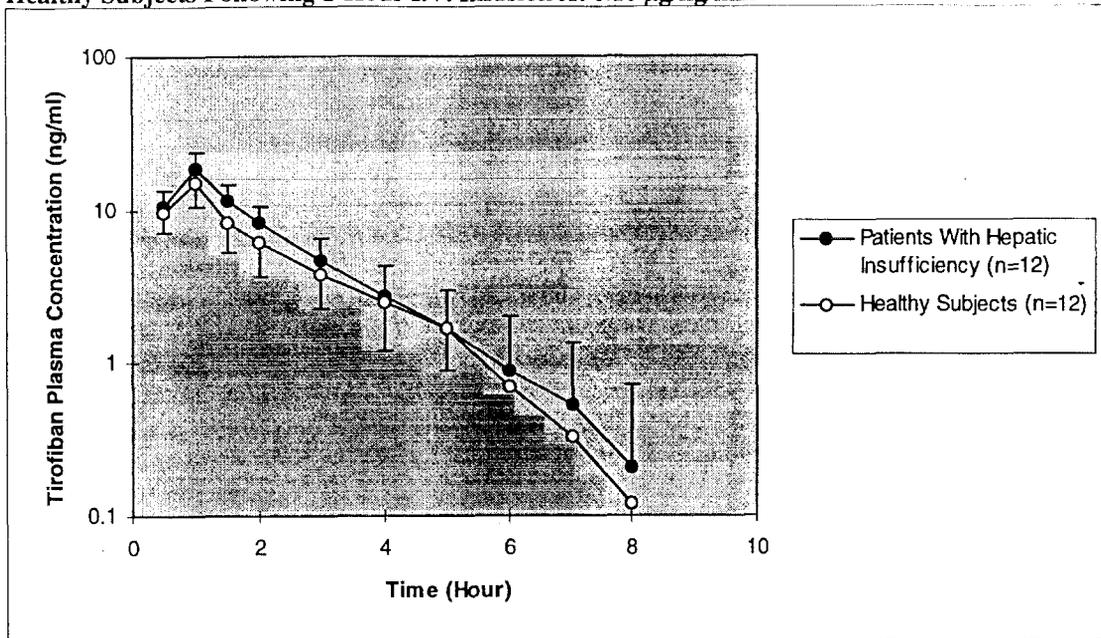
Table 8. Summary Of Mean (±SD) Pharmacokinetic Parameters In Healthy Subjects And Patients With Hepatic Insufficiency Following A 1-Hour I.V. Infusion (0.10 µg/kg/min) Of Tirofiban

Variable	Healthy Subjects	Patients With Hepatic Insufficiency	p-Value
	N=12	N=12	
CL (mL/min)	251.99±106.32	207.04±75.02	0.223
CL _r (mL/min)	143.03±37.32	129.01±31.83	0.333
CL _{nr} (mL/min)	108.96±83.53	78.02±51.73	0.287
t _{1/2} (hr) ^a	1.80±0.54	1.41±0.47	NA
λ (hr ⁻¹)	0.3844±0.1099	0.4908±0.1625	0.074
C _{1hr} (ng/mL)	15.119±4.48	18.93±5.26	NA
AUCT (ng·hr/mL)	28.32±10.08	36.52±12.75	NA
AUC _∞ (ng·hr/mL)	32.19±10.58	39.64±13.92	NA
Vd _{ss} (L)	33.71±14.54	21.94±3.95 ^b	0.013
Urinary Recovery _{0-24 hr} (µg)	252.14±83.29	302.77±81.15	NA
Urinary Recovery _{0-24 hr} (% dose) ^b	57.94±16.34	67.52±8.89	NA

[Sponsor's analysis. Adapted from NDA 20-912, Volume 47, Tables 3 & 4, pages 6785 & 6876. ^aHarmonic mean and pseudo SD. NA = not available]

Comparable plasma concentrations of Tirofiban over time were observed for both groups studied (Figure 10).

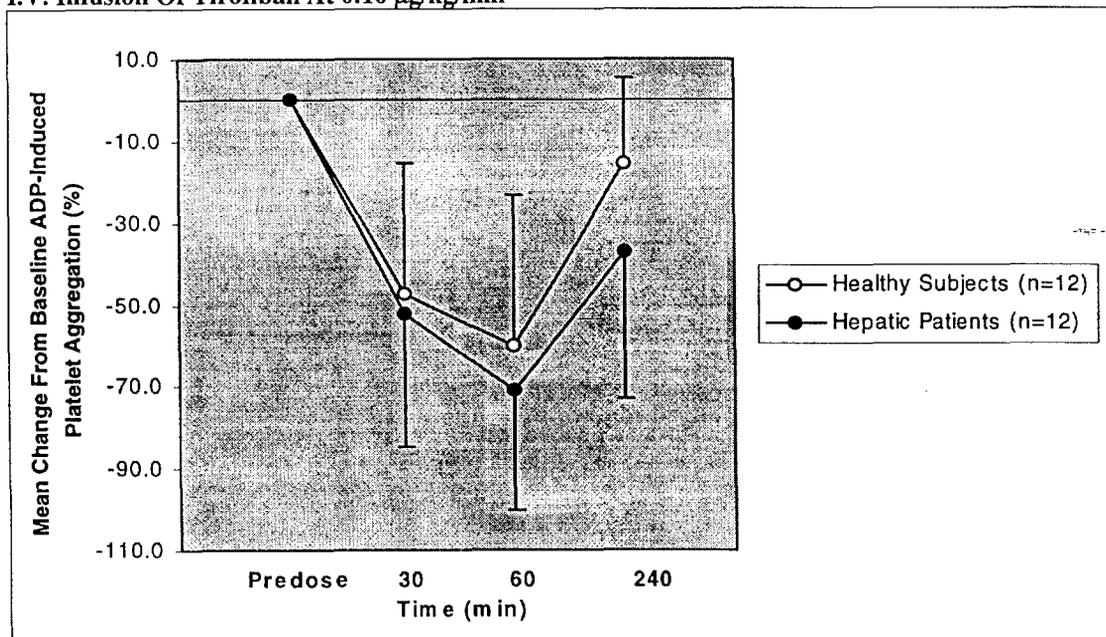
Figure 10. Mean (\pm SD) Concentrations Of Tirofiban In Plasma Of Patients With Hepatic Insufficiency And Healthy Subjects Following 1-Hour I.V. Infusion At 0.10 μ g/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 47, Tables 2, page 6795.]

The degree of inhibition of ADP-induced platelet aggregation achieved in healthy subjects and hepatic patients by Tirofiban administration was comparable (Figure 11).

Figure 11. Mean (\pm SD) Percent Change From Baseline ADP-Induced Platelet Aggregation Following 1-Hour I.V. Infusion Of Tirofiban At 0.10 μ g/kg/min



[Sponsor's analysis. Adapted from NDA 20-912, Volume 47, Tables 11, page 6751. At 240 min time point, healthy subjects = 8 & hepatic patients = 10.]

Bleeding time was assessed at screening and 180 minutes after initiation of Tirofiban infusion (Table 9). According to the sponsor, "there was no clinically significant difference in bleeding time in patients with hepatic insufficiency compared to control subjects."

Table 9. Mean^a (\pm SD) Bleeding Time (min) Following 1-Hour I.V. Infusion Of Tirofiban At 0.10 μ g/kg/min

Time	Healthy Subjects (n)	Hepatic Patients (n)
Prestudy	5.5 \pm 1.7 (12)	5.4 \pm 0.9 (12)
180 min	5.5 \pm 2.0 (6)	7.4 \pm 2.4 (8)

[Sponsor's analysis. Adapted from NDA 20-912, Volume 47, Tables 13, page 6755. ^aGeometric mean.]

SAFETY: None of the subjects/patients were discontinued because of a clinical adverse event. Adverse events were reported in two hepatic patients (AN 005 epistaxis; AN 008 confusion) and in three healthy subjects (An 013 headache; 018 paresthesia; An 019 headache). Hepatic patients AN 004 and 005 had an increase in fasting glucose.

There were no physical exam or vital sign adverse experiences reported or clinically significant deviations in serum chemistries during the study infusion period. One hepatic patient (AN 005) had a positive stool for occult blood predose and postdose.

CONCLUSIONS: Although one patient developed epistaxis, Tirofiban appears to be well tolerated by patients with hepatic insufficiency. The pharmacokinetic and pharmacodynamic results, from this small number of patients with moderate hepatic insufficiency, suggest that dose adjustments in this patient population may not be needed.

PROTOCOL NO.: 012

PROTOCOL TITLE: An Open Study In Healthy Male Subjects To Investigate The Disposition Of A Two-Hour I.V. Infusion of ¹⁴C-MK-0383 (Tirofiban)

To characterize the clinical pharmacology of Tirofiban, the disposition, metabolism and elimination of this compound were assessed by a 2-hour infusion of the ¹⁴C radioisotope.

STUDY DESIGN: This was an open, single-dose study in 6 healthy male subjects to investigate the distribution, metabolism, and elimination of a 2-hour i.v. infusion of [¹⁴C]-Tirofiban at 0.20 µg/kg/min. Throughout the study, the subjects were monitored for signs of clinical adverse experiences; safety was also assessed by the measurement of hematology, blood chemistry, and urinalysis parameters.

The main objectives of this study included: 1) to determine the distribution and elimination of [¹⁴C]-Tirofiban ; 2) to identify major metabolites, if any, of Tirofiban in humans; and 3) to examine the safety and tolerability of Tirofiban administered as a 2-hour i.v. infusion of 0.20 µg/kg/min.

RESULTS: The age of the six healthy male subjects, who entered and completed the study, ranged from 23 to 32 years. The relevant pharmacokinetic parameters of Tirofiban following an intravenous dose of its [¹⁴C] radioisotope are summarized in Table 10.

Table 10. Summary Of Mean^a (±SD) Pharmacokinetic Parameters Of [¹⁴C]-Tirofiban

Variable	Mean (±SD) N=6
CL (mL/min)	213.4±47.4
CL _r (mL/min)	144.3±20.1
CL _{nr} (mL/min)	69.1±35.2
C _{2hr} (ng/mL) ^b	46.4±15.5
t _{1/2} (hr) ^c	1.80±0.35
λ (hr ⁻¹)	0.385±0.072
AUCT (ng·hr/mL)	127.6±25.0
AUC _∞ (ng·hr/mL)	131.3±25.0
Vd _{ss} (L)	25.9±9.1
Urinary Recovery _{0-96 hr} (mg) ^d	1.12±0.18
Urinary Recovery _{0-96 hr} (% dose)	68.6±10.3

[Sponsor's analysis. Adapted from NDA 20-912, Volume 54, Table 3, page 10445. ^aArithmetic mean. ^b2-hour concentration. ^cHarmonic mean and pseudo SD. ^dThe mean dose given was 1.63±0.16 mg (94 µCi).]

Plasma radioactivity following i.v. administration of [¹⁴C]-Tirofiban was primarily accounted for by Tirofiban measured by radioimmunoassay. Metabolic profiling of the feces and urine indicated that unchanged Tirofiban represented ~90% and 80% of the total radioactivity, respectively.

SAFETY: There were only two patients who reported adverse experiences. Subject 004 complained of nausea and vomiting, and another subject 005 reported chills, headache, nausea and vomiting. According to the sponsor, there were no significant changes in vital signs, physical examinations, ECGs or laboratory values.

CONCLUSIONS: No safety concerns arise from this study. Tirofiban plasma concentrations declined rapidly with a half-life of 1.8 hours. The renal clearance of Tirofiban represents ~67% of the systemic clearance. In the aggregate, the data suggest limited metabolism of Tirofiban in man. There is marked excretion of unchanged Tirofiban in urine and feces, ~66 % and ~23%, respectively.

PROTOCOL NO.: 014**PROTOCOL TITLE: An Open-Label, One-Hour I.V. Infusion Study To Investigate The Pharmacokinetics, Safety, And Tolerability Of MK-0383 (Tirofiban) In Patients With Defined Degrees Of Renal Insufficiency**

Because the kidney significantly participates in the excretion of unchanged Tirofiban, this study intended to characterize its pharmacokinetics in patients with reduced kidney function. The sponsor proposed to use the results from this study in support of dosing recommendations.

STUDY DESIGN: Open-label, multicenter (EU), single-dose study in 9 healthy subjects and 22 patients with renal insufficiency⁷. Male and female subjects/patients between 24 and 69 years old, were randomized based on mean baseline creatinine clearance (CrCl) as follows: Group I = CrCl \geq 75 ml/min/1.73 m²; Group II = CrCl 30 to 60 ml/min/1.73 m²; Group III = CrCl \leq 29 ml/min/1.73 m²; Group IV = CrCl <10 ml/min/1.73 m² (patients undergoing hemodialysis). Pharmacokinetic parameters were determined by assaying plasma and urine specimens for Tirofiban. Platelet function, and its degree of inhibition, was determined by bleeding time⁸. Subjects/patients were monitored for adverse events throughout the study. Measurement of hematology, blood chemistry, and urinalysis parameters, before the study and after each treatment, also aided in the assessment of the safety of Tirofiban administration.

The objectives of the study were: 1) to determine the effect of renal dysfunction on the renal and systemic clearance of Tirofiban after an i.v. infusion dose of 0.10 μ g/kg/min⁹ for 1 hour; 2) to determine to what extent Tirofiban is cleared by hemodialysis; 3) to evaluate the safety and tolerability of a 1-hour i.v. infusion dose of Tirofiban in patients with renal insufficiency; and 4) to investigate in patients with renal insufficiency the effect of Tirofiban on bleeding time.

RESULTS: Demographic data including sex, age, race, and baseline creatinine clearance values and serum creatinine levels are summarized in Table 11. The age ranged from 30 to 68 years and from 24 to 69 years in the nine healthy subjects and in the twenty patients with renal dysfunction, respectively. Subjects/patients enrolled in the study were predominantly male and white.

Table 11. Demographics Of Subjects/Patients

Variable	Group I N=9	Group II N=8	Group III N=6	Group IV N=8
Male n(%)	6(66.6)	4(50)	5(83.3)	6(75)
Female n(%)	3(33.3)	4(50)	1(16.6)	2(25)
Age mean \pm SD	54.4 \pm 12.6	54.8 \pm 13.2	48.8 \pm 13.9	41.5 \pm 18.0
Race				
White n(%)	9(100)	8(100)	6(100)	6(75)
Other n(%)	0(0)	0(0)	0(0)	2(25)
Creatinine Clearance ^a mean \pm SD	107.63 \pm 24.08	40.09 \pm 9.97	13.73 \pm 5.23	-
Serum Creatinine ^b mean \pm SD	0.85 \pm 0.20	1.97 \pm 0.58	4.98 \pm 1.40	9.61 \pm 2.58

[Adapted from NDA 20-912, Volume 58, Table 4, pages 23 & 24. ^amL/min/1.73 m². ^bmg/dL.]

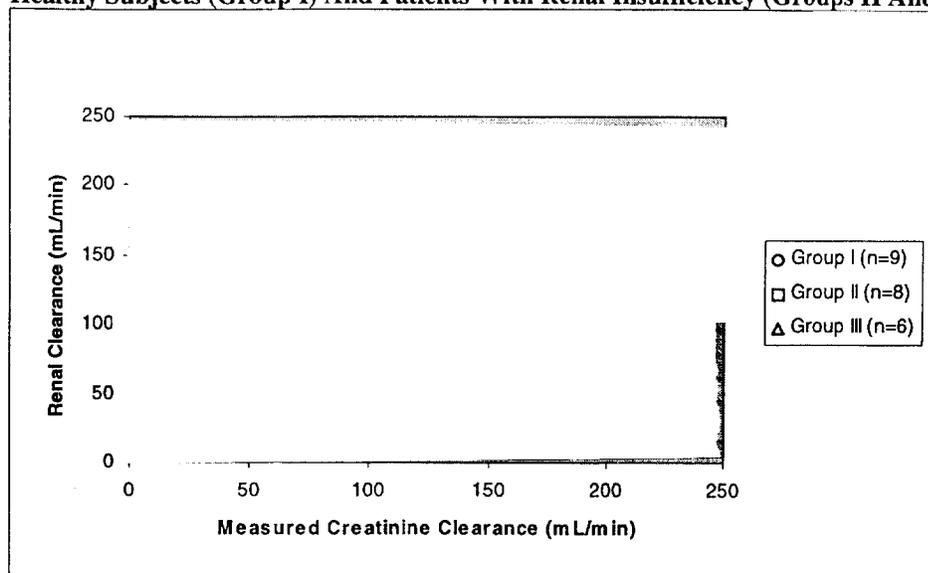
Pharmacokinetic and pharmacodynamic results are described in the following Figures and Tables. Figure 12 depicts the individual values of renal clearance of Tirofiban versus measured creatinine clearance for Groups I, II and III. There is a positive linear relationship between these two variables (Spearman's correlation = 0.95; Sponsor's analysis). This finding indicates a dependency of the renal component of the clearance of Tirofiban on glomerular filtration rate (i.e., creatinine clearance).

⁷ Detailed information on clinical observations and laboratory measurements obtained throughout the study is provided in NDA 20-912, Vol. 58, pages 13 and 14.

⁸ Bleeding time was performed using an automated template device.

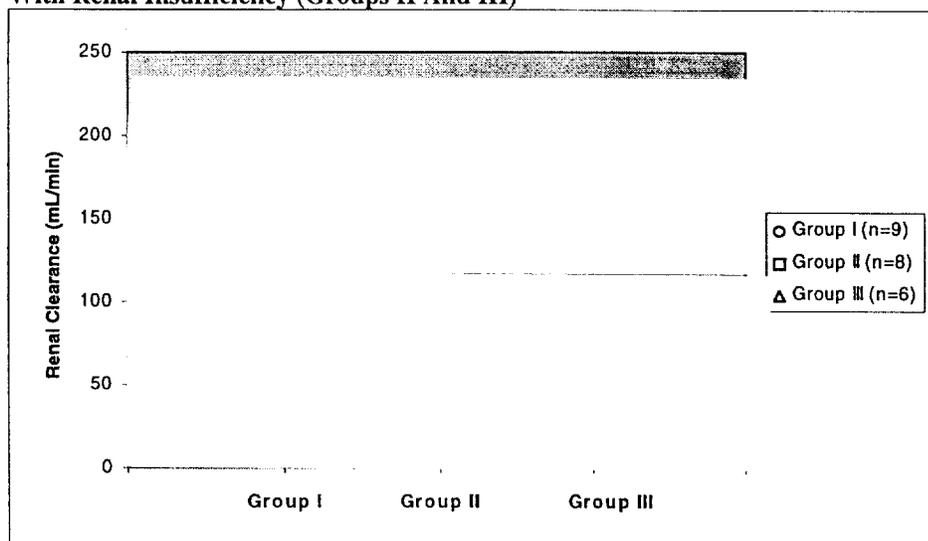
⁹ Due to evidence of increased pharmacologic effect (i.e., increased bleeding time), 3 Group IV patients received reduced doses of Tirofiban (0.05 μ g/kg/min; NDA 20-912, Vol. 58, pages 25 & 26).

Figure 12. Individual Values Of Renal Clearance Of Tirofiban Versus Measured Creatinine Clearance In Healthy Subjects (Group I) And Patients With Renal Insufficiency (Groups II And III)



In Figure 13 the individual values of the renal clearance of Tirofiban in healthy subjects (Group I) and in patients with distinct degrees of renal insufficiency (Groups II and III) are depicted. As expected, lower levels of kidney function are associated with lower renal clearances of Tirofiban. The geometric means calculated by the sponsor for the renal clearance in Groups I, II and III were 165.4 mL/min, 42.7 mL/min, and 11.2 mL/min, respectively (data not shown). Of note, the renal clearance in Group I was significantly less than in Groups II and III ($p < 0.01$), and Group III renal clearance was significantly lower than in Group II ($p < 0.01$; Sponsor's analysis). As was the case with the renal clearance, a direct correlation was also established between systemic clearance of Tirofiban and creatinine clearance (Spearman's correlation = 0.79; Sponsor's analysis¹⁰).

Figure 13. Individual Values Of Renal Clearance Of Tirofiban In Healthy Subjects (Group I) And Patients With Renal Insufficiency (Groups II And III)



¹⁰ NDA 20-912, Vol. 58, Figure 5, pages 35 and 36.

The individual values of non-renal clearance of Tirofiban in healthy subjects (Group I) and in patients with reduced creatinine clearance are summarized in Figure 14. The means of non-renal clearance of Tirofiban in Groups I, II, III, and IV were 340.4 mL/min, 150.9 mL/min, 91.7 mL/min, and 130.1 mL/min, respectively. The non-renal clearance was significantly higher in Group I than in the other three groups¹¹. In the aggregate, the data suggest that the non-renal clearance of Tirofiban might also be influenced by the level of renal function (i.e., glomerular filtration rate).

Figure 14. Individual Values Of Non-Renal Clearance Of Tirofiban In Healthy Subjects (Group I) And Patients With Renal Insufficiency (Groups II, III, and IV)

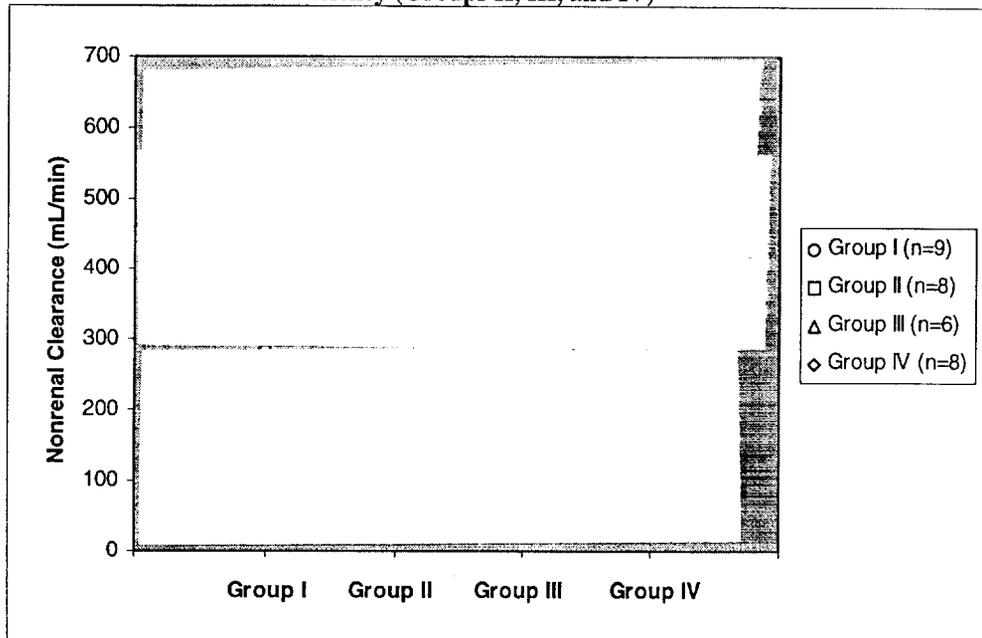


Table 12 summarizes relevant pharmacokinetic parameters such as systemic clearance (CL), renal clearance (CL_r), non-renal clearance (CL_{nr}), half-life (t_{1/2}), elimination rate constant (λ), volume of distribution at steady state (Vd_{ss}), and urinary recovery.

The t_{1/2} was significantly prolonged in patients with renal dysfunction as compared to healthy subjects. In Group I t_{1/2} was significantly lower than in Groups II, III and IV¹². AUC_∞ was significantly higher in patients with renal dysfunction Groups II, III and IV than in the healthy subjects from Group I.¹³

¹¹ P-Value^a Results Of Comparisons Of Non-Renal Clearance Among Groups

	Group I vs II	Group I vs III	Group I vs IV	Group II vs III	Group II vs IV	Group III vs IV
p-Value	0.012315	0.0056	0.00782	0.038009	0.540448	0.258297

[^aTwo-Sample equal variance, FDA's analysis. CL_{nr} assumed equal to CL in Group IV.]

¹² P-Value^a Results Of Comparisons Of T_{1/2} Among Groups

	Group I vs II	Group I vs III	Group I vs IV	Group II vs III	Group II vs IV	Group III vs IV
p-Value	0.000343	3.44E-05	0.000445	0.010579	0.026799	0.852

[^aTwo-Sample equal variance, FDA's analysis.]

¹³ P-Value^a Results Of Comparisons Of AUC_∞ Among Groups

	Group I vs II	Group I vs III	Group I vs IV	Group II vs III	Group II vs IV	Group III vs IV
p-Value	0.000303	0.002204	0.02927	0.083188	0.415202	0.551365

[^aTwo-Sample equal variance, FDA's analysis.]

Results indicate that Tirofiban is dialyzable, the mean dialysis clearance of Tirofiban, in patients from Group IV undergoing hemodialysis (a 4-hour dialysis period), was 73.4 mL/min. The volume of distribution at steady state was similar among the Groups.

Table 12. Summary Of Mean^a (±SD) Pharmacokinetic Parameters Of Tirofiban By Renal Group

Variable	Group I N=9	Group II N=8	Group III N=6	Group IV N=8
CL (mL/min)	513±183	202±71	103±30	130±75
CL _r (mL/min)	172±37	51±25	12±4	-
CL _{nr} (mL/min) ^b	340±180	151±57	92±28	-
Dialysis Clearance (mL/min)	-	-	-	73.4±19.0 ^c
t _{1/2} (hr) ^d	0.96±0.28	1.9±0.6	3.4±0.9	3.0±1.9
λ (hr ⁻¹)	0.719±0.203	0.357±0.108	0.206±0.057	0.228±0.0125
AUCT (ng·hr/mL)	15±8.1	41.7±14.8	75.7±47.6	-
AUC _∞ (ng·hr/mL)	17.4±8.4	46.3±16.3	82.3±51.1	-
Vd _{ss} (L)	35.5±7.0	32.0±6.8	27.9±3.8	31.3±11.8
Urinary Recovery _{0-48 hr} (μg)	213±108	141±47	50±24	-
Urinary Recovery _{0-48 hr} (% dose)	44.7±17.7	27.8±7.7	11.2±3.5	-

[Sponsor's analysis. Adapted from NDA 20-912, Volume 58, Table 7, page 28. ^aArithmetic mean. ^bCL_{nr} assumed equal to CL in Group IV. ^cObtained during dialysis period 2; two subjects received a reduced dose of 0.05 μg/kg/min. ^dHarmonic mean and pseudo SD.]

Another objective of the study was to investigate in patients with renal insufficiency the effect of Tirofiban on bleeding time (Table 13). Of note, 3 patients from Group IV received 50% of the protocol dose.

Table 13. Mean (±SD) Bleeding Time Following A 1-Hour Infusion Of Tirofiban In Healthy Subjects (Group I) And Patients With Renal Insufficiency (Groups II, III, and IV)

Time	Group	Bleeding Time ^a (min)
Prestudy	I (n=9)	5.8±1.7
	II (n=9)	5.4±2.1
	III (n=9)	4.5±2.5
	IV (n=9)	4.4±1.8
4 Hr	I (n=9)	6.2±1.7
	II (n=9)	5.6±1.7
	III (n=9)	7.7±4.5
	IV ^a (n=9)	9.5±10.1
	IV ^b (n=9)	5.3±4.0

[Sponsor's analysis. Adapted from NDA 20-912, Volume 58, Table 17, page 13022. ^aGeometric mean±SD. ^bNondialysis day. ^cDialysis day.]

SAFETY: No subject/patient had a serious adverse event or discontinued due to a clinical adverse experience. According to the sponsor "no clinically important changes between prestudy and poststudy physical examinations, vital signs, and ECGs were noted." Table 14 lists the subject/patient that experienced adverse events and/or laboratory abnormalities.

Table 14. List Of Subjects/Patients With Adverse Events And/Or Laboratory Abnormalities

Group	Patient ID#	Sex	Averse Event
I	041	M	Vomiting, syncope
I	001	M	Light headedness
I	002	F	Light headedness
I	003	M	Headache, vomiting
I	005	M	Vomiting
I	028	F	Hematoma
II	008	M	Headache
II	009	F	Headache (frontal), decreased platelet count ¹⁴
II	010	M	Headache (frontal), nausea, vomiting, abdominal pain, light headeness
II	012	F	Abdominal fullness, diarrhea
II	030	M	Headache, gout
III	013	M	Headache, jaw stiffness, dry mouth, vomiting, diarrhea
III	033	M	Hemoccult positive
III	051	M	Diarrhea, increased bleeding time (27 min, 1/24) ^a
IV	038	M	Nausea
IV	042	M	Increased bleeding time (35 min, 2/4) ^a , increased urine RBCs
IV	057	F	Increased bleeding time (49 min, 2/4) ^a
IV	058	M	Increased bleeding time (32 min, 2/4) ^a

[Sponsor's analysis. Adapted from NDA 20-912, Volume 58, Tables 12 & 14, pages 13018-13020. ^aMaximum bleeding time, period/hour post infusion.]

CONCLUSIONS: The results from this study indicate that the renal clearance of Tirofiban is significantly modified by the degree of renal dysfunction (Table 12). Furthermore, the data suggest that the nonrenal clearance of Tirofiban may also be altered (i.e., reduced) in patients with renal insufficiency compared to subjects with normal renal function (Table 12). However, the latter statement needs to be corroborated. Hemodialysis data supports the concept that Tirofiban is dialyzable. Bleeding time was prolonged from baseline values in patients requiring hemodialysis and in some patients from Group III (creatinine clearance ≤ 29 ml/min/1.73 m²).

Other than one patient with decreased platelet count and the changes in bleeding time already mentioned above, no clinically important adverse events were reported with the administration of Tirofiban in this study.

Albeit in the aggregate, the data supports the conclusion that Tirofiban's dosing should be reduced in patients with renal dysfunction, it is not clear to this reviewer at what level of renal function a reduction is necessary and by what percentage the recommended dose should be reduced. On the basis of the results of this study the sponsor proposes "that the dose should be reduced by 50% in patients with creatinine clearance values of less than 30 ml/min."

¹⁴ Platelet Counts

	Prestudy	Predose	4-Hr	24-Hr	120-Hr	336-Hr
Platelet count (GIGA/L)	314	410	285	240	151	293

[Sponsor's analysis. Adapted from NDA 20-912, Volume 58, Tables 15, page 54.]