

Table 1.4/ Other Sponsor's ITT Analysis Results for Some Secondary Endpoints

Endpoint	Time Point	Incidence Rate		% Difference		CMH 2-Sided
		Frag	Plac	(F-P)*	95% CI	P-value
Need for iv Heparin	Day 6	3.8%	7.7%	-3.9	(-6.3, -1.5)	0.001
	Day 40	8.4%	13.6%	-5.2	(-8.4, -2.0)	0.001
	Day 150	11.9%	16.7%	-4.8	(-8.4, -1.2)	0.008
Need for iv Nitroglycerine	Day 6	4.9%	9.3%	-4.4	(-7.0, -1.8)	0.001
	Day 40	12.7%	17.1%	-4.4	(-8.1, -0.8)	0.015
	Day 150	17.7%	22.4%	-4.7	(-8.8, -0.5)	0.023
Incidence of Revascularization	Day 6	0.4%	1.2%	-0.8	(-1.7, 0.1)	0.070
	Day 40	12.1%	15.5%	-3.4	(-7.0, -0.1)	0.039
	Day 150	32.9%	35.5%	-2.6	(-7.5, 2.4%)	0.221
Incidence of Ischemia	Day 6	45.5%	50.5%	-5.0	(-10.8, 0.8)	0.097
	Day 40	40.3%	42.6%	-2.3	(-8.7, 4.1)	0.421
	Day 150	not provided				

Difference = (Fragmin - Placebo) incidence rates; CMH = Cochran-Mantel-Haenszel

Table 1.5/ Sponsor's Subgroup ITT Analysis Results Through Day 6: Incidence of Death and/or MI

Subgroup		Fragmin		Placebo		% Difference	CMH
		Rate	%	Rate	%	Frag - Plac	P-val
Sex:	Female	2/271	0.7	14/268	5.2	-4.5	0.004
	Male	11/470	2.3	22/489	4.5	-2.2	0.093
Age (years):	≤70	7/422	1.7	20/399	5.0	-3.4	0.018
	>70	6/319	1.9	16/358	4.5	-2.6	0.070
Weight:(Kg):	≤70	1/250	0.4	13/246	5.3	-4.9	0.002
	>70	12/491	2.4	23/511	4.5	-2.1	0.093
High Risk:	Yes	1/184	0.5	10/198	5.3	-4.5	0.012
	No	12/557	2.2	26/559	4.7	-2.5	0.026
Previous MI:	Yes	3/213	1.4	12/224	5.4	-3.9	0.039
	No	10/528	1.9	24/533	4.5	-2.6	0.016
Smoking:	Smoker/Smoked	6/398	1.5	20/394	5.1	-3.6	0.012
	Never Smoked	7/343	2.0	16/363	4.4	-2.4	0.090
Inclusion Event:	Unstable Angina	6/452	1.3	19/472	4.0	-2.7	0.016
	Non-Q-Wave MI	7/288	2.4	17/284	6.0	-3.6	0.036
# of Anti-angina Drugs:	0	4/332	1.2	10/328	3.0	-1.8	0.077
	1	7/219	3.2	12/224	5.4	-2.2	0.319
	≥2	2/190	1.1	14/205	6.8	-5.8	0.003

CMH = Cochran-Mantel-Haenszel test

4.0 Summary of Efficacy Results

Sponsor's analysis results for the primary overall composite endpoint (*death and/or MI*) summarized in Tables 1.3-1.5 above suggest Fragmin has a significant short-term (Day 1-6) and borderline long-term (Day 6-40) advantage over placebo in reducing the incidence of death and/or myocardial infarction (MI). That is, for the

- (i) primary time-point Day 6, Fragmin is shown to be superior to placebo in reducing the incidence of death and/MI in the treatment of unstable angina or non-Q-Wave MI to prevent ischemic complications in patients on concomitant aspirin therapy (see Table 1.3 above),
- (ii) secondary time-points Day 40, Fragmin appears to have a borderline

advantage over placebo in reducing the incidence of death and/MI in the treatment of unstable angina or non-Q-Wave MI to prevent ischemic complications in patients on concomitant aspirin therapy (see Table 1.3 above),

- (iii) secondary time-point Day 150, however, Fragmin appears to only hold a slight numerical edge over placebo in reducing the incidence of death and/MI in the treatment of unstable angina or non-Q-Wave MI to prevent ischemic complications in patients on concomitant aspirin therapy (see Table 1.3 above)
- (iv) For subgroups such as gender, age (≤ 70 , >70 years old), weight (≤ 70 , >70 lbs.), and risk factors such as previous MI, smoking history, and inclusion events, sponsor's efficacy analysis results are consistent with the overall efficacy results summarized above. That is, the data suggest a short-term (Day 1-6) but no long-term Fragmin advantage over placebo (see Table 1.5A attached),
- (v) Similar results are observed for secondary endpoints such as need for intravenous heparin and nitroglycerine. Regarding the incidence of ischemia and revascularization, however, Fragmin is shown to have no more than a slight numerical advantage over placebo (see Table 1.4 above).

4.1.0 REVIEWER'S COMMENTS

4.1.1 Database For Primary Efficacy Analysis & Missing Data

The SAS data set submitted by the sponsor contained about 10 patients less than the data set used for the primary efficacy analysis by the sponsor, as can be seen in Table 1.6 below. A comparative summary of the missing rates between Fragmin and placebo at each time point for all the randomized patient cohort (exposed to both Fragmin 120IU and 150IU), and for the patient cohort exposed to Fragmin 120IU or matching placebo only is given in Table 1.7 below.

Table 1.6/Patient Disposition: SAS Data Set vs. Sponsor's Analysis Data Set

	Sponsor Reported/Analyzed Data Set: Total Exposed: 1622 (116 + 1506)		Sponsor Submitted SAS Data Set: Total Exposed: 1612 (114+1498)	
	Fragmin	Placebo	Fragmin	Placebo
Randomized:	809	813	802	810
Exposed to 150IU	63	53	61	53
Exposed to 120IU/Analyzed	746/741	760/757	741	757

Data from sponsor Tables 25-34; Vol. 2 & submitted SAS Data set floppy diskette

Notice that there were numerically more missing evaluations/observations in the Fragmin than in the placebo treatment group at each of the three time point for

both the all randomized patient cohort and the patient cohort exposed to Fragmin 120IU or matching placebo only. For time point Day 150, these differences were statistically significantly different for both the all randomized patient cohort and for the patient cohort exposed to Fragmin 120IU or matching placebo only.

Table 1.7/Proportion of Patients with Missing Evaluations/Data (As Per SAS Data Set)

Submitted SAS Data Set: Total Exposed: 1612 (114 on 150IU+ 1498 on 120IU) Frag. or Placebo				
	Fragmin	Placebo	Difference#	P-valu*
All Randomized :				
Day 6	7/802 (0.87%)	3/810 (0.37%)	0.50	0.115
Day 40	10/798 (1.25%)	5/808 (0.62%)	0.63	0.089
Day 150	23/786 (2.93%)	11/802 (1.37%)	1.56	0.014
Exposed to 120IU:				
Day 6	5/741 (0.67%)	2/757 (0.26%)	0.41	0.159
Day 40	7/738 (0.95%)	3/755 (0.40%)	0.55	0.112
Day 150	20/726 (2.75%)	3/749 (0.40%)	2.35	<.001

Data from sponsor submitted SAS Data set; #: Difference = Frag - Plac; *: p-values are 2-sided Fisher's exact.

The observed incidence rates as per SAS data set for all three patients cohorts (those exposed to Fragmin 150IU or matching placebo only, those exposed to Fragmin 120IU or matching placebo only, and those exposed to both Fragmin 150IU, and 120IU or matching placebo) are summarized in Table 1.8 below.

The first column of this table summarizes the observed incidence rates in the cohort of patients exposed to Fragmin 150IU or matching placebo. Except for time point Day 6 (where Fragmin had a slight numerical edge over placebo), Fragmin was (at least numerically) out-performed by placebo at time points Day 40 and Day 150, as can be seen by the positive treatment difference (Fragmin - placebo). The corresponding 2-sided p-values (not included in the Table 1.8) on differences in proportions are 0.945, 0.069 and 0.154, respectively.

For the cohort of patients exposed to Fragmin 120IU only (second column of table below), note that the incidence rates are identical to those summarized in Table 1.3.

The combined incidence rates for the two cohorts (*Fragmin 150 IU versus matching placebo and Fragmin 120 IU versus matching placebo*) are summarized in the third column of Table 1.8 below. For the combined events, the results are again consistent with those summarized in Table 1.3 above. That is, Fragmin is still shown to be superior to placebo for the primary time point Day 6 (2-sided Cochran-Mantel-Haenszel (CMH) p-value = 0.0025). For the secondary time points Day 40 and Day 150, the results are again similar to those summarized in Table 1.3 above.

Table 1.8/ Incidence Rates For Primary Efficacy Endpoints (as Per SAS Data Set)

114 Patients Exposed To Fragmin 150IU			1498 Patients Exposed To Fragmin 120IU			Combined Incidence Rate (150IU + 120IU)		
Placebo	Fragmin	F - P	Placebo	Fragmin	F - P	Plac (%)	Frag (%)	F-P
3/53 (5.7%) ⁶	3/61 (4.9%)	-0.8	36/757(4.8%)	13/741 (1.8%)	-3.0	39/810(4.8)	16/802(2.0)	-2.6
3/53 (5.7%) ⁴⁰	9/60(15.0%)	9.3	81/755(10.7%)	59/738 (8.0%)	-2.7	84/808(10.4)	68/798(8.5)	-1.9
6/53(11.3%) ¹⁵⁰	13/60(21.7%)	10.4	116/749(15.5%)	102/726(14.1%)	-1.4	122/802(15.2)	115/786(14.6)	-0.6

6=Time point Day6; 40 = time point Day 40; 150 = time point Day 150.

4.1.2 Adjustment of Efficacy Results for Missing Data

Assuming missing evaluations are in fact events/failures (worst case scenario). Table 1.9 below summarizes the estimated incidence rates for the all randomized patient cohort (patients exposed to Fragmin 150IU or Fragmin 120IU or matching placebo) and the cohort of patients exposed to Fragmin 120IU or matching placebo only.

Table 1.9/Estimated Incidence rates with Missing Treated as Events (as Per SAS Data Set)

Submitted SAS Data Set: Total Exposed: 1612 (114 + 1498)				
	Fragmin	Placebo	Difference	P-value*
All Randomized :				
Day 6	23/802 (2.87%)	42/810 (5.19%)	-2.32	0.020
Day 40	78/798 (9.77%)	87/808 (9.89%)	-0.12	0.513
Day 150	148/786 (17.56%)	125/802 (15.59%)	+1.97	0.087 ^a
Exposed to 120IU or placebo:				
Day 6	18/741 (2.43%)	39/757 (5.15%)	-2.72	0.007
Day 40	66/738 (8.94%)	86/755 (11.39%)	-2.45	0.119
Day 150	122/726 (16.80%)	127/749 (16.96%)	-0.16	0.938

*: P-values are 2-sided CMH; Data from sponsor submitted SAS Data set;

a: p-value indicates superiority of placebo over Fragmin; Difference = Fragmin - Placebo.

In both cohorts, the superiority of Fragmin over placebo for the primary time-point Day 6 is still strongly supported. The results for the all randomized patient cohort indicate a numerical placebo edge over Fragmin at the secondary time-point Day 150, while Fragmin is shown to hold a numerical edge over placebo at time point Day 40.

4.1.3 Contribution of Components of the Composite Endpoints

Table 1.10 below summarizes the efficacy results as per each component of the composite primary endpoint. Note that for the patient cohort exposed to Fragmin 120IU or matching placebo (assuming missing are not events), Fragmin is shown to be superior to placebo in reducing MI, and numerically better in reducing deaths at the time point Day 6 (see Table 1.10 below).

Thus each component of the composite endpoint appears to play a major role in the observed significant findings for the primary time-point Day 6. The results for

the secondary time points Day 40 and Day 150 for each component of the composite endpoint are consistent with those observed for the composite endpoint at these time points. This observed apparent Fragmin advantage is lost upon factoring in missing rates (according to the worst case scenario adjustment for missing data). Note that in the table below, missing observations for death and MI are the same since a missing observation for the composite endpoint implied both death and MI were missing.

Table 1.10/ Incidence Rates among Cohort Exposed to Fragmin 120IU/kg/12hr

Time	Placebo	MI		Death		
		Fragmin	Frag - Pla	Placebo	Fragmin	Frag - Pla
Observed						
Day 6	33/754(4.38%)	10/738(1.36%)	-3.02	8/754(1.06%)	7/741(0.94%)	-0.12
Day 40	72/746(9.65%)	49/728(6.73%)	-2.95	23/755(3.05%)	19/737(2.56%)	-0.49
Day 150	98/731(13.41%)	83/707(11.74%)	-1.67	41/747(5.49%)	38/725(5.38%)	-0.11
Missing						
Day 6	3/53 (5.67%)	5/61 (8.20%)	+2.53	3/53 (5.67%)	5/61 (8.20%)	+2.53
Day 40	5/53 (9.43%)	7/59 (11.86%)	+2.43	5/53 (9.43%)	7/59 (11.86%)	+2.43
Day 150	11/53 (20.75%)	20/59 (33.90%)	+13.15	11/53 (20.75%)	20/59 (33.90%)	+13.15
Combined(O+M)						
Day 6	36/754 (4.77%)	15/738 (2.03%)	-2.77 ¹	11/754 (1.46%)	12/741 (1.62%)	+0.16
Day 40	77/746 (10.32%)	56/728 (7.69%)	-2.63 ²	28/755 (3.70%)	26/737 (3.52%)	-0.18 ³
Day 150	109/731 (14.91%)	103/707 (14.56%)	-0.35 ²	52/747 (6.96%)	58/725 (8.00%)	+1.04

O = observed incidence rate, M = assumed incidence rate for missing data; Difference = Placebo - Fragmin;

¹: Two-sided CMH p-value = .054; ²: two-sided CMH p-value = .079; ³: two-sided CMH p-value > 0.500.

Note: +ve difference indicates a placebo numerical edge over Fragmin.

Table 1.11 below summarizes similar events for the patient cohort exposed to Fragmin 150IU only. Except for MI at time point Day 6 (where Fragmin appears to a numerical edge over placebo), Fragmin 150IU/kg/12hr was numerically worse than placebo at the other two (secondary) time points.

Table 1.11/ Incidence Rates among Cohort Exposed to Fragmin 150IU/kg/12hr Only

Time	Placebo	MI		Death		
		Fragmin	Frag - Pla	Placebo	Fragmin	Frag - Pla
Observed						
Day 6	3/53 (5.56%)	3/61 (4.92%)	-0.74	0/53 (0.0%)	1/61 (1.64%)	+1.64
Day 40	3/53 (5.56%)	7/58 (12.07%)	+6.51	0/53 (0.00%)	5/59 (8.47%)	+8.47
Day 150	6/53 (11.32%)	9/56 (16.07%)	+4.75	0/53 (0.00%)	9/59 (15.25%)	+15.25
Missing						
Day 6	0/53 (5.56%)	2/61 (3.28%)	+3.28	0/53 (0.00%)	2/61 (3.28%)	+3.28
Day 40	0/53 (0.00%)	3/59 (5.08%)	+5.08	0/53 (0.00%)	3/61 (5.08%)	+5.08
Day 150	0/53 (0.00%)	3/59 (5.08%)	+5.08	0/53 (0.00%)	3/61 (5.08%)	+5.08
Combined(O+M)						
Day 6	3/53 (5.56%)	5/61 (8.20%)	+2.64	0/53 (0.00%)	3/61 (4.92%)	+4.92
Day 40	3/53 (5.56%)	10/59 (16.95%)	+11.39	0/53 (0.00%)	8/61 (13.11%)	+13.11
Day 150	6/53 (11.32%)	12/59 (20.34%)	+9.02	0/53 (0.00%)	12/61 (19.67%)	+19.67

O = observed incidence rate, M = assumed incidence rate for missing data; Difference = Placebo - Fragmin.

Note: +ve difference indicates a numerical placebo edge over Fragmin.

Table 1.11A (attached) summarizes incidence rates by center. Note that rates are consistent across centers; Breslow-Day (BD) test for common odds ratios across centers for time point Day 6 failed to reject the null hypothesis of uniform treatment effect across centers (BD p-value=0.743, treatment effect CMH p-value = 0.992; see bottom of table).

Similar results (regarding test of homogeneity of odds ratios) are obtained for Day 40 (BD p-value for common odds ratios = 0.722; CMH p-value for treatment effect = 0.202), and for Day 150 (BD p-value for common odds ratios = 0.802, and CMH for treatment effect = 0.735).

5. Summary of Safety Events

The protocol specified safety objective of this study was to determine the safety of Fragmin compared with placebo regarding the incidence of bleeding, allergic reactions, and thrombocytopenia following 45 days of treatment. Tables 1.12 and 1.13 below contain comparative summaries of some safety events in this study for the cohort of patients who received Fragmin 150 IU/kg or matching placebo (Table 1.12), and the cohort of patients who received Fragmin 120 IU/kg or matching placebo (Table 1.13).

Table 1.12/Safety Events Summary for Fragmin 150 IU/kg (From Sponsor Tables 87 and 88, Vol. 2)

Safety Variable	Phase I (Event Rate)			Phase II (Event Rate)		
	Fragmin 150	Placebo	Fra - Pla	Fragmin 150	Placebo	Fra - Pla
All Bleed	4/63(6.3)	0/53 (0.0)	+6.3	1/49 (2.0)	0/46 (0.0)	+2.0
Major Bleed	9/63(14.3)	0/53 (0.0)	+14.3*	4/49 (8.2)	2/46 (4.3%)	+3.9
Minor Bleed	0/63 (0.0)	0/53 (0.0)	0.0	1/50 (2.0)	0/46 (0.0)	+2.0
T Cytopenia ¹	0/63 (0.0)	0/53 (0.0)	0.0	0/50 (0.0)	1/46 (2.2)	0.0

*: Fisher's exact 2-sided p-value < ; Data from sponsor submitted SAS Data set; ¹: T Cytopenia = Thrombocytopenia

Table 1.13/Safety Events Summary for Fragmin 120 IU/kg (From Sponsor Tables 87 and 88, Vol. 2)

Safety Variable	Phase I (Event Rate)			Phase II (Event Rate)		
	Frag 120	Placebo	Fra - Pla	Frag 120	Placebo	Fra - Pla
Major Bleed	6/746(0.8)	4/760(0.5)	+0.3	2/616 (0.3)	1/613 (0.2)	+0.1
Minor Bleed	60/746(8.0)	2/760(0.3)	+7.7*	39/616(6.3)	17/613 (2.8%)	+3.5*
T Cytopenia ¹	0/743 (0.0)	2/755 (0.3)	-0.3	0/613 (0.0)	0/610 (0.0)	0.0
A Reactions	2/746 (0.3)	0/760 (0.0)	+0.3	6/617 (1.0)	6/614 (1.0)	0.0

*: Fisher's exact 2-sided p-value <0.004; Data from sponsor submitted SAS Data set;

¹: T Cytopenia = Thrombocytopenia, A Reactions = Allergic Reactions.

Except for minor bleeding, there were no significant safety differences between Fragmin and placebo (in either phase of the study). For minor bleeding, however, there were significantly more events in the Fragmin (both Fragmin 150 and 120 IU/kg infusions) than in the placebo group of patients.

Note that the entry age to this study was 40 years or older. The pediatric implication of this drug is therefore not clear to this reviewer.

6. FRIC [INTERNATIONAL STUDY #CTN 91-128]

6.0 STUDY DESIGN

This trial was conducted as an international study (in nine countries) between March 1993 and June 1995. It was designed as a 2-Phase, randomized, open-label, active control (*Phase I*), and non-randomized, double blind, placebo control (*Phase II*), parallel group, multicenter study. Of the 150 centers originally planned, 83 actually enrolled patients into the study.

6.1 Study Objectives

The primary objective of this study was to compare the (long-term) efficacy of LMWH Fragmin with placebo regarding the incidence of cardiac events [i.e., *death, acute myocardial infarction (MI), and/or recurrence of angina*] following 6-45 days (*Phase II*) of treatment for unstable coronary artery disease (CAD).

Secondary objectives of the study include:

- 1) Comparing the efficacy of Fragmin with heparin regarding the incidence of cardiac events and revascularization, as well as frequency of ischemia during exercise testing on day 6 following 1-6 days of treatment (*Phase I*).
- 2) Comparing the efficacy of Fragmin with placebo in *Phase II* of the study (6-45 days of treatment) and until 3-month follow-up regarding the incidence of cardiac events and revascularization, as well as frequency of ischemia during exercise testing on day 45.
- 3) Comparing efficacy in relation to *Phase I* treatment (Fragmin versus heparin) on incidence of cardiac events in *Phase II* (Day 6-45)
- 4) Comparing the safety of Fragmin with placebo regarding the incidence of bleeding complications, death, allergic reactions, and thrombocytopenia following 45 days of treatment.

6.2 Study Plan

Patients who satisfied the inclusion criteria were randomized into the trial on **Day 1** to receive either Fragmin or heparin. The trial was divided into two phases:

Phase I: This was a weight adjusted treatment phase; randomized patients received either Fragmin 120 IU/kg/12hr sc or heparin 5000 IU/bolus iv +1000 IU/h for 1-6 days. Heparin administration was to start with an initial iv bolus dose of 5000 IU, followed within two hours, by a 1000 IU/hour continuous iv dose, and daily thereafter.

- Day 1:** Patients were randomized and received the first injection, APTT (heparin group).
- Day 2:** Resting ECGs, APTT (heparin group), Anti-FXa (Fragmin group), lab tests for haemoglobin, thrombocytes.
- Day 3-5:** Patients instruction and training for performing self-injection of study drug, APTT (heparin group).
- Day 6 (5-8):** Resting ECGs, exercise tests, APTT (heparin group), Anti-FXa (Fragmin group), and lab tests for haemoglobin, thrombocytes, unused ampoules study drug documented, and treatment with *Phase II* study drug started. Treatment with *Phase II* drug was started.

Phase II: Randomized patients from *Phase I* received (in a non-randomized manner, as per NDA documentation) a fixed dosing regimen of Fragmin 7500 IU or matching placebo every 24 hours. Resting ECGs and exercise tests were performed at Day 6 and Day 45, APTT (heparin group), Anti-FXa (Fragmin group) were taken at Day 6, and lab tests for haemoglobin and thrombocytes were done at Day 6 and Day 45. Clinical data were documented; patient diaries were checked, and both used and unused syringes were counted, and saved on **Day 45** (40-50).

Phase III: This was a 3-month follow-up period following 45 days of treatment. Resting ECGs were to be taken, and clinical data documented.

Note that all patients were to be treated with aspirin (ASA) 100-165 mg daily throughout the duration of the study, unless they were hypersensitive to ASA.

NDA documentation indicated that the concept for the design of this study was based mainly from the clinical experience gained in the RISC trial. Heparin was selected as the control group for the open-label phase (*Phase I*) because it is frequently used in the treatment of UCAD. Placebo was selected as the control for the double blind phase (*Phase II*) because heparin effect seemed to disappear when discontinued in the RISC-trial.

6.3 Inclusion criteria

Inclusion criteria included a minimum age of 40 years, postmenopausal period of at least 12 months for females, admission to coronary care unit for chest pain with a last chest pain episode within 72 hours before start of treatment, fulfillment of at least one of the following anamnestic conditions:

- newly developed angina pectoris during the last two months,
- increased angina pectoris during the last two months,
- ongoing chest pain, with a suspicion of MI,

and fulfillment of at least one of the following ECG criteria without any other explanation than myocardial ischemia:

- temporary or manifest ST-depression with at least 0, 1 mV ($\geq 1\text{mm}$) in at least two adjacent leads, and
- temporary or manifest T-inversion with at least 0, 1 mV ($\geq 1\text{mm}$) below the baseline in at least two adjacent leads.
- Informed consent.

7. SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

7.0 Primary efficacy Endpoint

The primary efficacy endpoint is a composite endpoint comprising *the first occurrence of death, myocardial infarction (MI), or recurrence of angina*. Death was defined as all-cause mortality and where possible, the cause was to be established by post-mortem examination. MI was to be confirmed by diagnostic ECG series or by at least two of the following: prolonged angina chest pain, separate diagnostic ECG, and significant rise in relevant enzymes (CK, CK-MB, CK-B or ASAT/ALAT). Recurrence of angina was defined as restart of nitroglycerine infusion due to anginal chest pain (*Phase I*); hospitalization and restart of nitroglycerine or heparin infusion due to chest pain (*Phase II*).

A number of secondary endpoints including *revascularization* and *ischemia* during exercise test are specified.

7.1 Sample Size Estimation

Assuming a 40% withdrawal rate due to cardiac events in *Phase I* of the study and a 5% two-sided test with 80% power, the protocol indicated that approximately 1500 patients were to be enrolled into the study. This was based on the assumption that with cardiac event, or recurrence of angina incidence rates of 10% and 5% for placebo and Fragmin, respectively, in the second phase of the study, significant treatment difference would be detected with 434 patients per *Phase II* treatment group.

7.2 Randomization & Blinding

Patients were randomized (once in *Phase I*) in a 1:1 ratio to receive (*in an open-label manner*) either subcutaneous Fragmin 120 IU/kg BID by body weight or heparin for 1-6 days. In *Phase II* of the study, patients from each treatment arm were assigned in a *double blind, non-random* manner to either subcutaneous Fragmin 7500 IU or matching placebo once daily for 6-45 days.

The protocol indicated that qualifying patients were given consecutive patient numbers on entering the study. Randomization (in *Phase I*) was based on a computer-generated codes by a SAS program written at the [REDACTED]

Randomization was done separately within each participating country (*Austria, Spain, UK, Germany, the Netherlands, Canada, US, Italy and Norway*) in blocks of size 4, 8, 12 or 16 depending on the estimated number of patients to be included. Randomization was done 29 times with separate randomization number series per center. For the double blind (*Phase II*) phase of the study, a patient was to receive a medical box containing Fragmin or placebo with the same number as the patient number. *Treatment allocation was decided (non-randomly) at the*

Randomization Problems (Phase I)

Random numbers were generated for 150 centers; 83 of these participated and actually enrolled patient(s) into the study. NDA documentation indicated the following randomization errors:

- Forty three (43) patients numbers (from 17 different centers) were omitted due to practical mistakes, 16 patients were randomized but did not receive study drug, and one patient received only *Phase II* study drug.
- Randomization was done out of sequence in center #s 10, 12, 13, 16, 73, 74, 80, 96, 125 and 142. The affected patients were not excluded from the analysis.
- Center #114 used the study drug originally assigned to center 115 (patient numbers 11501-11505) in order to enroll additional patients (center 115 never started); use of these random numbers from center 115 was approved by the Study Director.
- Patient 12503 received the *Phase II* study drug for patient 1502 (placebo), and patient 12504 received the *Phase II* study drug for patient 12503 (placebo). Both patients were included in the ITT but not in the per-protocol analyses as per study drug received in *Phase II*.
- Eight patients (4205, 5411, 5818, 6101, 7314, and 8020) received the wrong study medication in Phase I. All except patient 5506 and 7704 were included in the ITT analyses; all eight were excluded from the per protocol analyses.

Blinding: The protocol indicated that *Phase II* study drugs were packed and labeled in a double blind fashion. The syringes used for both placebo and Fragmin were identical in appearance so that neither the investigator, patient, Clinical Monitor nor the Study Director was aware of the allocation of treatment until clean file was declared.

7.3 Statistical Methods

The primary objective of this study was to compare the incidence of cardiac events between Fragmin and placebo during the second phase of the study (*Day 6-45*), given that there were no events during the first phase (*Day 1-6*). The primary analysis for the composite primary endpoint (for *Day 6-45*) was done (as per protocol specification) using the Cochran-Mantel-Haenszel (CMH) test; 95% confidence intervals (CIs) were provided. Test of homogeneity of treatment effect across centers was performed using the Breslow-Day (BD) test.